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Iron Catalyzed Selective Nitrogen Atom Transfer Reactions for Olefin Difunctionalization: Iron Catalyzed Direct Diazidation and Asymmetric Intramolecular Aminohydroxylation of Olefin

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IRON CATALYZED SELECTIVE NITROGEN ATOM TRANSFER REACTIONS FOR OLEFIN DIFUNCTIONALIZATION: IRON CATALYZED DIRECT DIAZIDATION AND ASYMMETRIC INTRAMOLECULAR AMINOHYDROXYLATION OF OLEFIN

by

YONGAN YUAN

Under the Direction of Hao Xu (Ph.D.)

ABSTRACT

Numerous biologically active alkaloids and pharmaceuticals contain nitrogen atoms that are directly attached to stereogenic centers. Therefore, selective nitrogen atom transfer to readily available hydrocarbons through novel mechanistic pathways is an important tool for the synthesis of high-value functional molecules. We are interested in direct difunctionalization of alkenes with non-precious iron catalyst due to its advantages over well-established olefin aziridination and direct C-H amination methods in organic synthesis. Herein, we describe iron-catalyzed nitrogen atom-transfer methods for stereoselective olefin difunctionalization, including olefin aminohydroxylation and diamination reactions. These transformations capitalize on the

novel reactivity of iron catalysts by conveniently converting petrochemicals to highly functionalized building blocks that are valuable to organic synthesis, materials, and biomedical sciences.

The first chapter of the dissertation gives an overview of ligand design and iron catalyst discovery for selective nitrogen atom-transfer to alkenes. The ligand can combine with a metal center through chelation to afford an asymmetric catalyst. This asymmetric catalyst can thus be used to transfer its chirality to its corresponding enantiopure product from achiral precursors. [Fe(**L1**)$(OTf)_2$], [Fe(**L2**)$(OTf)_2$], [Fe(**L3**)$(OAc)_2$] and [Fe(**L4**)$(NTf_2)_2$] complexes were synthesized and reactivity studies of these iron complexes were performed.

The second chapter of the dissertation describes an iron(II)-catalyzed intramolecular aminohydroxylation of olefins with functionalized hydroxylamines. A diastereoselective aminohydroxylation of olefins with a functionalized hydroxylamine is catalyzed by new iron(II) complexes. This efficient intramolecular process readily affords synthetically useful amino alcohols with excellent selectivity (*dr* up to > 20:1). Asymmetric catalysis with chiral iron(II) complexes and preliminary mechanistic studies reveal an iron nitrenoid is a possible intermediate that can undergo either aminohydroxylation or aziridination, and the selectivity can be controlled by careful selection of counteranion/ligand combinations.

The third chapter describes an iron(II)-catalyzed asymmetric intramolecular aminohydroxylation of indoles. An enantioselective intramolecular indole aminohydroxylation reaction is catalyzed by iron(II) chiral bisoxazoline (BOX) complexes (*ee* up to 99%, *dr* > 20:1). This discovery enables expedient asymmetric synthesis of a series of biologically active 3-amino oxindoles and 3-amino indolanes.

The fourth chapter focuses on iron(II)-catalyzed direct diazidation for a broad range of olefins. This novel reaction occurs at room temperature (1–5 mol% of catalysts and *dr* values of up to >20:1). This method tolerates a broad range of both unfunctionalized and highly functionalized olefins, including those that are incompatible with existing methods. It also provides a convenient approach to vicinal primary diamines as well as other synthetically valuable nitrogen-containing building blocks which are difficult to obtain with alternative methods. Preliminary mechanistic studies suggest that the reaction may proceed through a new mechanistic pathway in which both Lewis acid activation and iron-enabled redox catalysis are crucial for selective azido-group transfer.

INDEX WORDS: Iron catalysis, Direct alkene difunctionalization, Selective nitrogen atom-transfer, Asymmetric synthesis, Aminohydroxylation and diamination, Natural product synthesis

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Office of Graduate Studies

College of Arts and Sciences

Georgia State University

May 2016

DEDICATION

To my mom, Zhenping Wang, who always kept me away from the street and provided me the opportunity to chase my dreams. Although we are a thousand miles away, as my personal inspiration and beliefs, she has been my momentum in conquering all that comes against me and making me ready for the new challenges in life. There are not enough words to express how much I love you. I cannot go this far without your support and you are the real "MVP" in my heart.

I also dedicate this work to my beloved wife, Zhuo Wang, works as hard as me day in day out without complaint. Your love makes me stronger to overcome the obstacles; your encouragement inspires me to make a more intellectual contribution; your kindness creates the only place where I find inner peace in life. I love your curves and edges, and all your perfect imperfections.

Last but not least, to my son little walnut, who I could never meet. If there were any chance mama and papa could just take one glance you, we would like to trade everything we have for that without hesitation. You had only been in this world for 79 days and suffered a lot of pain not owing to you. My son, the only thing I want to let you know is that you have your life together with us at the moment you left us; you are not alone no matter where you are and what you do. May you rest in peace and we love you forever.

ACKNOWLEDGEMENTS

To pursue a doctoral career is one of the most important decisions that I have made in my first thirty years. Upon graduation, I want to sincerely acknowledge all those people who helped me with this dissertation.

First and foremost, I would like to give my gratitude to my advisor, Dr. Hao Xu, who encouraged and supported me in both academics and mentality throughout my graduate study. His detailed-oriented attitude, as well as the scientific spirit of seeking positive discovery from unpolished raw data, elevates me to an advanced level of viewing scientific research. As a senior and brilliant young scientist, he sets a model example for us to learn and develop. I appreciate the opportunity he gave me to join his research team and to be a part of the group.

I am indebted to all the faculties of GSU chemistry department for the very best support. Especially, Dr. Alfons Baumstark, you are an icon not only to me but also to our chemistry department. I still remember those hard times you gave me during the class, group meeting as well as my thesis dissertation. However, when I look back over my graduate studies, believe it or not, those are the only very few things I can clearly pick up and share with my family. "There are no stupid chemists, there are only lazy people." "I can teach a monkey to do NMR" I will keep my good work attitudes that you taught me no matter where I go and what I do in the future. I wish you and Barbara long happy and healthy life. I want to thank Dr. Jun Yin for his great questions with my presentation, patient discussions as well as helpful advice. It's a big fortune for us to have you join our GSU big family. I also appreciate Dr. Ivaylo Ivanov for his detailed discussions and valuable suggestions towards the computational modeling study of my iron nitrene and azido radical chemistry. I appreciate all your time in reviewing my thesis and providing me the fruitful advice.

I would like to say many thanks to my past and present group members and all the people I tutored or worked with. Dr. Guansai Liu, as my first senior mentor, led me into the world of organic chemistry and worked with me side by side on the iron-catalyzed intramolecular aminohydroxylation reaction project. Dr. Yongqiang Zhang, who is now an Alexander von Humboldt Scholar in Germany, I wish you all the best in your future endeavors. You are more than a mentor to me, but a big brother and a lifelong friend. My techniques and knowledge in the field of organic chemistry were explosively expanded because of your detailed instruction and criticism day in day out. Our indole project would not have been such a big success without your hard work and output, which laid a solid foundation for my own independent work. Dr. Dengfu Lu, you are an amazing scientist and critical film fan. I benefited a lot from every discussion with you, and your deep thought in each and every project earns our respect. I am 100% sure that you will be a big professor in a top tier university in the very near future. Chengliang Zhu, a rising young star scientist that I am so proud of being your peer. You always hold my back with your signature warm smile. Thanks for everything you have done for me and our whole group. I am also grateful to Dr. Cheng Wang for his very generous help, especially the discussions in synthesis, spectral analysis and structural elucidation; to my friend Garrett Edmunds for proofreading my manuscript; to Jeff Sears for taking most of our group maintenance jobs; to Dr. Junshan Tian and Dr. Yunrong Chen for their encouragement and help. All my friends in the chemistry department at Georgia State Univeristy deserve my deepest respect and gratitude.

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1.1 INTRODUCTION

1.1.1 Chiral Ligands in Asymmetric Catalysis

Chiral ligands are specially designed and widely adapted molecules utilized for asymmetric synthesis. The chiral ligand which is enantiopure can coordinate with a metal center through chelation to afford an asymmetric catalyst. This asymmetric catalyst can thus be used to transfer its chirality to the reaction product in a chemical reaction. The beauty of chiral ligand in asymmetric catalysis is that even catalyst at low concentration is effective to turn over much more equivalents of reactant to its corresponding enantiopure product from the achiral precursor, making it superior to most chiral auxiliaries and well suited to large scale synthesis.

1.1.2 Chiral and C_2-Symmetrical Box Ligands

Interestingly, although thousands of chiral ligands have been synthesized and screened, some of these are enantioselective over a wide range of different reactions. We call such catalysts "privileged ligands".[1] Examples of privileged chiral ligands and catalysts are listed in Figure **1** below. The framework of Bis(oxazoline) ligands inspired by vitamin B_{12}, was first synthesized and used for enantioselective carbenoid cyclopropanation in 1984 by Brunner.[2] Later, in 1989, Nishiyama reported the first application of tridentate nitrogen ligand PyBox in transition metal catalysis.[3] These newly designed chiral ligands were simply prepared from 2,6-Pyridinedicarboxylic acid and enantiopure amino alcohols, drawing significant attention due to

the ready availability of chiral precursors and their excellent performance in hydrosilylation of ketones, oxidative cyclization, reductive cyclization of various unsaturated alkyl halides, etc.[3-4] Iron-based catalysts is less explored compared with the noble metals, such as Pd, Pt, Ru as well as Rd. Therefore, the discovery of a novel iron-based catalyst is of great importance due to its high abundance, low cost, and low toxicity.[5] Fe/PyBox complexes were developed for a broad range of organic transformations such as the asymmetric Nazarov cyclization,[6] asymmetric aziridine formation reaction,[7] Mukaiyama-Aldol reaction,[8] etc. Based on the X-ray crystallographic analysis and reactivity studies of these Fe-PyBox complexes, we learned that the coordination abilities of pybox ligands to the iron center as well as the reactivities of the Fe-PyBox complexes were dependent on the structure of the pybox ligand employed.[9]

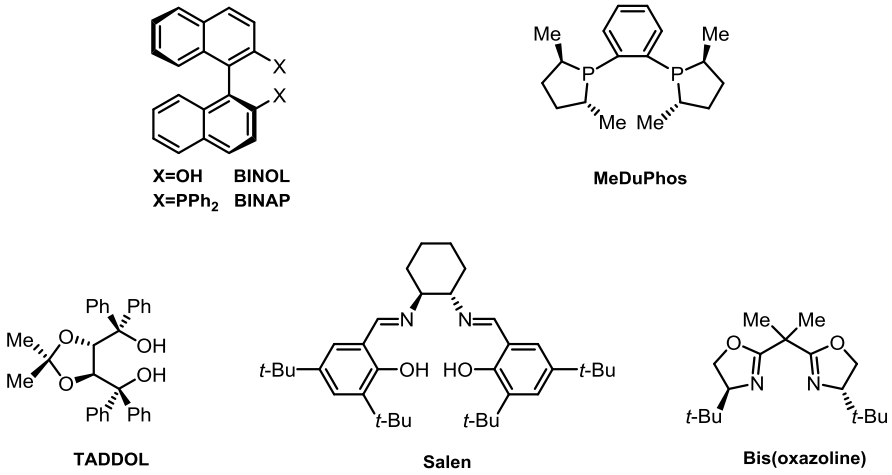


Figure 1. Privileged Chiral Ligands

1.1.3 Expected Results

We are interested in discovering general and selective catalytic reactions that transform readily available hydrocarbons to high-value functional molecules through novel mechanistic pathways. One of our current research focuses is to develop iron-catalyzed nitrogen atom transfer methods for stereoselective olefin functionalization, including olefin aminohydroxylation, and

diamination reactions. These transformations capitalize on the novel reactivity of iron catalysts by conveniently converting petrochemicals to highly functionalized building blocks that are valuable to organic synthesis, material and biomedical sciences.

1.2 EXPERIMENT

1.2.1 General Information

General Procedures. All reactions were performed in oven-dried or flame-dried round-bottom flasks and vials. Stainless steel syringes and cannula were used to transfer air- and moisture-sensitive liquids. Flash chromatography was performed using silica gel 60 (230-400 mesh) from Sigma–Aldrich.

Materials. Commercial reagents were purchased from Sigma-Aldrich, Fluka, EM Science, and Lancaster and used as received. All solvents were used after being freshly distilled unless otherwise noted.

Instrumentation. Proton nuclear magnetic resonance (^{1}H NMR) spectra， carbon nuclear magnetic resonance (^{13}C NMR) spectra and fluorine nuclear magnetic resonance (^{19}F NMR) were recorded on Bruker UltraShield-400 (400 MHz). Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to the NMR solvent residual peak ($CHCl_3$: δ 7.26). Chemical shifts for carbons are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$: δ 77.0). Chemical shifts for fluorine are reported in parts per million downfield and are referenced to the fluorine resonances of $CFCl_3$. Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz), and integration.

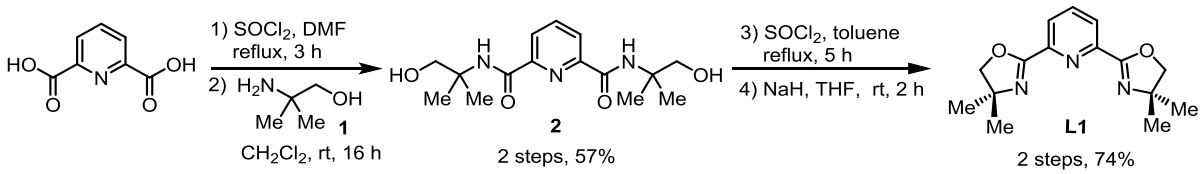
The mass spectroscopic data were obtained at the Georgia State University mass spectrometry facility using a Micromass Platform II single quadruple instrument. Infrared (IR) spectra were obtained using a Perkin Elmer Spectrum 100 FT-IR spectrometer. Data are represented as follows: frequency of absorption (cm^{-1}) and absorption strength (s = strong, m = medium, w = weak).

Abbreviations used: EtOH–ethanol, EtOAc–ethyl acetate, THF–tetrahydrofuran, MeOH–methanol, Et2O–diethyl ether, CH2Cl2–dichloromethane, TEA–triethylamine, MeCN–acetonitrile, MS–molecular sieves, CDI–1,1′-carbonyl diimidazole, Troc–2,2,2-trichloroethoxycarbonyl, DCC–N,N′-dicyclohexylcarbodiimide, TLC–thin layer chromatography, Boc_2O–di-tert-butyl dicarbonate, DMAP−4-dimethylaminopyridine.

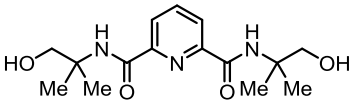
1.2.2 Synthesis of Fe-TetraMe PyBox Complex

1.2.2.1 Synthesis of TetraMe PyBox Ligand

Ligand **L1** was synthesized according to a modified literature procedure:[10]

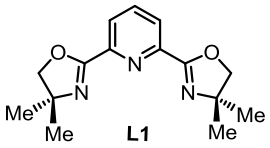


Scheme 1. Synthesis of TetraMe PyBox Ligand



To a 100 mL flame-dried flask charged with a stir bar and a reflux condenser was added 2,6-pyridinedicarboxylic acid (3.34 g, 20 mmol). After the flask was evacuated and backfilled with N_2 twice, $SOCl_2$ (30 ml) and DMF (0.2 mL) were added. The reaction was heated under a

reflux condition for 3 h. Then the mixture was cooled to room temperature and concentrated *in vacuo* to afford the 2,6-pyridinedicarbonyl dichloride as a white solid which can be used directly in the next step. Under N_2 atmosphere, to a solution of amino alcohol **1** (6.23g, 70 mmol) and Et_3N (10.1g, 100 mmol) in CH_2Cl_2 (70 mL), were added 2,6-pyridinedicarbonyl dichloride in CH_2Cl_2 (30 mL) drop-wise at 0 °C. After the reaction mixture was stirred at room temperature for 16 h, the mixture was poured into an ice-water mixture (60 mL), which was then extracted with CH_2Cl_2 (60 mL × 3). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified through a silica gel flash column (hexanes/acetone: from 10:1 to 1:1) to afford product **2** as a white solid (3.53 g, 57% yield for 2 steps), which is a known compound.[10]

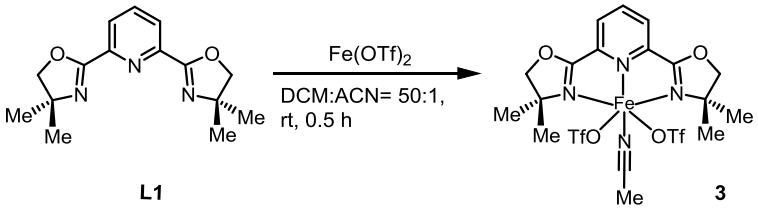


L1

2 (3.09 g, 10 mmol) was dissolved in toluene (40 mL) in a 100 mL flame-dried flask charged with a stir bar and a reflux condenser. $SOCl_2$ (7.14 g, 60 mmol) was added via a syringe and the mixture was heated under a reflux condition. The reaction was monitored by TLC. When the starting material disappeared, the reaction was cooled to 0 °C and quenched with a saturated $NaHCO_3$ solution (30 mL). The organic layer was separated from the aqueous one which was then extracted with EtOAc (30 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was filtered through a short silica gel pad with EtOAc as an eluent and concentrated again. The obtained oil was dissolved in anhydrous THF (50 mL) under N_2 atmosphere and cooled to 0 °C. NaH (2 g, 50 mmol, 60% in mineral oil) was added to the solution portion-wise and the whole mixture was then warmed up to room temperature and monitored by TLC until the starting material was fully consumed. The reaction

mixture was filtered through a Celite pad, concentrated and purified through a silica gel flash column (hexanes/acetone: from 20:1 to 2:1) to provide the ligand **L1** as a white solid (2.02 g, 74% yield for 2 steps).

1.2.2.2 Synthesis of Fe-TetraMe PyBox complex



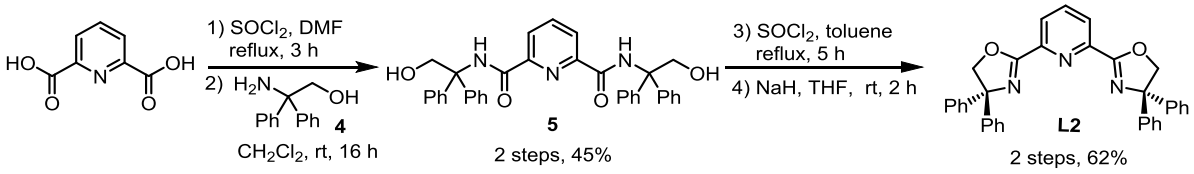
Scheme 2. Synthesis of Fe-TetraMe PyBox Complex

Iron complexes **3** was prepared by stirring iron(II) triflate anhydrous and the corresponding PyBox ligand at a ratio of 1:1 in DCM/MeCN (50:1) at room temperature (Scheme **2**). Upon removal of the solvent *in vacuo,* iron complex **3** was achieved in almost quantitative yield.

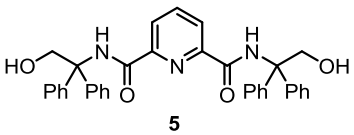
1.2.3 Synthesis of Fe-TetraPh PyBox Complex

1.2.3.1 Synthesis of TetraPh PyBox Ligand

Ligand **L2** was synthesized according to a modified literature procedure:

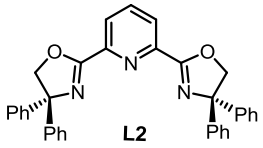


Scheme 3. Synthesis of TetraPh PyBox Ligand



To a 100 mL flame-dried flask charged with a stir bar and a reflux condenser was added

2,6-pyridinedicarboxylic acid (3.34 g, 20 mmol). After the flask was evacuated and backfilled with N_2 twice, $SOCl_2$ (30 ml) and DMF (0.2 mL) were added. The reaction was heated under a reflux condition for 3 h. Then the mixture was cooled to room temperature and concentrated *in vacuo* to afford the 2,6-pyridinedicarbonyl dichloride as a white solid which can be used directly in the next step. Under N_2 atmosphere, to a solution of amino alcohol **4** (6.23g, 70 mmol) and Et_3N (10.1g, 100 mmol) in CH_2Cl_2 (70 mL), were added 2,6-pyridinedicarbonyl dichloride in CH_2Cl_2 (30 mL) drop-wise at 0 °C. After the reaction mixture was stirred at room temperature for 16 h, the mixture was poured into an ice-water mixture (60 mL), which was then extracted with CH_2Cl_2 (60 mL × 3). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified through a silica gel flash column (hexanes/acetone: from 10:1 to 1:1) to afford product **5** as a white solid (5.01 g, 45% yield for 2 steps), which is a known compound.[10, 11]

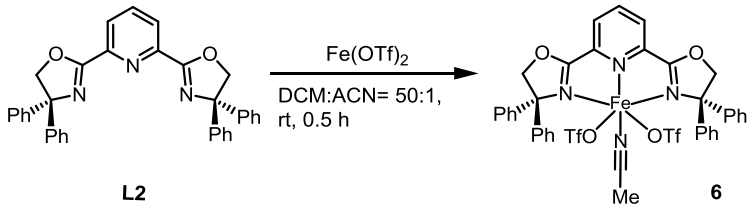


L2

5 (5.01 g, 9 mmol) was dissolved in toluene (40 mL) in a 100 mL flame-dried flask charged with a stir bar and a reflux condenser. $SOCl_2$ (6.43 g, 54 mmol) was added via a syringe and the mixture was heated under a reflux condition. The reaction was monitored by TLC. When the starting material disappeared, the reaction was cooled to 0 °C and quenched with a saturated $NaHCO_3$ solution (30 mL). The organic layer was separated from the aqueous one which was then extracted with EtOAc (30 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was filtered through a short silica gel pad with EtOAc as an eluent and concentrated again. The obtained oil was dissolved in anhydrous THF (50 mL) under N_2 atmosphere and cooled to 0 °C. NaH (1.8 g, 45 mmol, 60% in mineral oil) was

added to the solution portion-wise and the whole mixture was first warmed up to room temperature and then was refluxed until TLC indicated fully consumption of the starting material and reaction intermediate. The reaction mixture was filtered through a Celite pad, concentrated and purified through a silica gel flash column (hexanes/acetone: from 20:1 to 2:1) to provide the ligand **L1** as a white solid (2.90 g, 62% yield for 2 steps).

1.2.3.2 Synthesis of Fe-TetraPh PyBox Complex

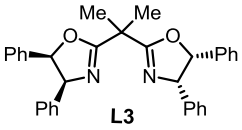


Scheme 4. Synthesis of Fe-TetraPh PyBox Complex

Iron complexes **6** was prepared by stirring iron(II) triflate anhydrous and the corresponding PyBox ligand at a ratio of 1:1 in DCM/MeCN (50:1) at room temperature (Scheme **4**). Upon removal of the solvent in vacuo, iron complex **6** was achieved in almost quantitative yield.

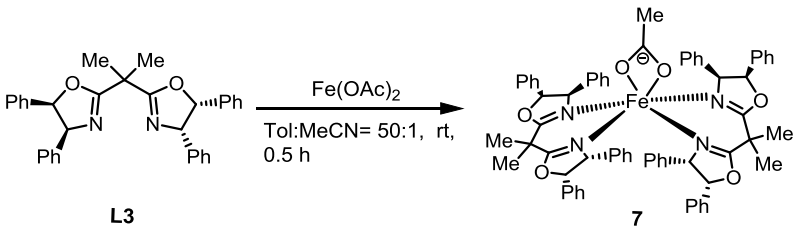
1.2.4 Synthesis of Fe-TetraPh Box Complex

1.2.4.1 Synthesis of TetraPh Box Ligand



L3 was synthesized according to the literature procedures.[12]

1.2.4.2 Synthesis of Fe-TetraPh Box Ligand

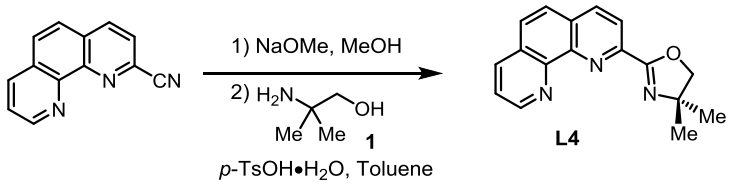


Scheme 5. Synthesis of Fe-TetraPh Box Complex

Iron complexes **7** was prepared by stirring iron(II) acetate anhydrous and the corresponding Box ligand at a ratio of 1:2 in Tol/MeCN (50:1) at room temperature (Scheme **5**). Upon removal of the solvent in vacuo, iron complex **7** was achieved in almost quantitative yield.

1.2.5 Synthesis of Fe-Phenanthroline Box Complex

1.2.5.1 Synthesis of Phenanthroline Box Ligand

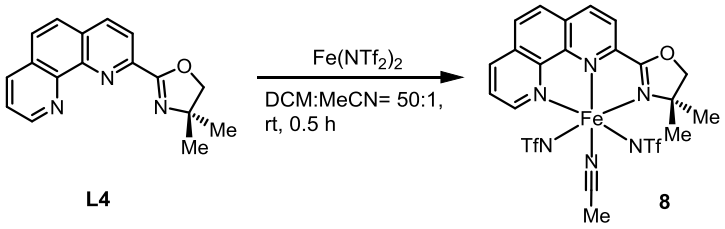


Scheme 6. Synthesis of Phenanthroline Box Ligand

Ligand **L4** was synthesized from 2-cyanophenanthroline.[13] 2-Cyanophenanthroline (4.10g, 20 mmol) was dissolved in anhydrous methanol (60 mL) in a flame-dried flask equipped with a stir bar. NaOMe (108 mg, 2 mmol) was added to the reaction. The reaction mixture was stirred at room temperature and monitored with TLC until the starting material was fully consumed. The reaction was then quenched with acetic acid (0.22 mL) and the mixture was filtered and concentrated *in vacuo*. The residue was dissolved in toluene (100 mL) together with amino alcohol **1** (1.87 g, 21 mmol) and *p*-TsOH·H_2O (380 mg, 2 mmol). The reaction mixture was then heated under a reflux condition with a Dean−Stark apparatus until the intermediate was consumed. After the reaction was cooled to room temperature, the solvent was removed *in vacuo*

and the residue was purified through a silica gel flash column (hexanes/acetone: from 2:1 to 1:2) to afford **L4** as a white solid (3.6g, 65% yield).[10]

1.2.5.2 Synthesis of Fe-Phenanthroline Box Complex



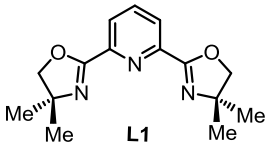
Scheme 7. Synthesis of Fe-Phenanthroline Box Complex

Iron complexes **8** was prepared by stirring iron(II) triflimide and the corresponding Box ligand at a ratio of 1:1 in DCM/MeCN (50:1) at room temperature (Scheme **7**). Upon removal of the solvent in vacuo, iron complex **8** was achieved in almost quantitative yield.

1.3 RESULTS

1.3.1 Results of Fe-TetraMe PyBox Complex

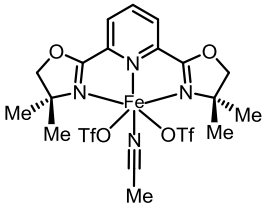
1.3.1.1 Results of TetraMe PyBox Ligand



2,6-Bis(4,4-dimethyl-4,5-dihydrooxazol-2-yl)pyridine (**L1**): ligand **L1** was further purified by recrystallization from a mixture of hexanes/EtOAc (9:1) as a colorless crystalline solid (m.p. 139–141 °C). IR ν_{max} (neat)/cm^{-1}: 3423 (w), 2967 (m), 2927 (w), 2896 (w), 1641 (s), 1573 (s), 1459 (s), 1365 (s), 1302 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, J = 7.9 Hz, 2H),

7.87 (t, *J* = 7.9 Hz, 1H), 4.24 (s, 4H), 1.42 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9, 147.0, 137.1, 125.7, 79.8, 68.0, 28.4; HRMS (ESI, m/z): calcd for $C_{15}H_{20}N_3O_2^+$, [M + H^+], 274.1550, found 274.1554.

1.3.1.2 Applications of Fe-TetraMe PyBox Complex

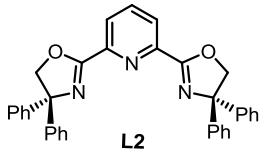


3

Complex **3** shows new reactivity in effectively catalyzing intermolecular olefin amino hydroxylation, amino halogenation as well as diazidation reactions.

1.3.2 Results of Fe-TetraPy PyBox Complex

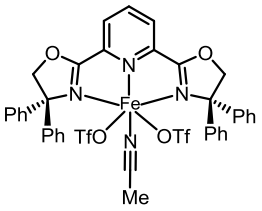
1.3.2.1 Results of TetraPh PyBox Ligand



L2

2,6-Bis(4,4-diphenyl-4,5-dihydrooxazol-2-yl)pyridine (**L2**): white solid (m.p. 213–215 °C); IR ν_{max} (neat)/cm^{-1}: 3059 (w), 3026 (w), 1641 (s), 1570 (m), 1492 (m), 1449 (s), 1380 (s), 1114 (m), 1077 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (d, *J* = 7.8 Hz, 2H), 7.92 (t, *J* = 7.8 Hz, 1H), 7.40 (d, *J* = 7.9 Hz, 8H), 7.33 (t, *J* = 7.5 Hz, 8H), 7.26 (t, *J* = 7.2 Hz, 4H), 5.09 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.7, 146.9, 145.7, 137.2, 128.5, 127.3, 126.7, 126.7, 80.5, 79.8; HRMS (ESI, m/z): calcd for $C_{35}H_{28}N_3O_2^+$, [M + H^+]: 522.2176, found 522.2178.

1.3.2.2 Applications of Fe-TetraPh PyBox Complex

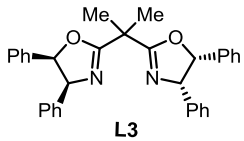


6

Complex **6** is effective to catalyze highly diastereoselective intermolecular diazidation reaction for a broad range of olefins.

1.3.3 Results of Fe-TetraPy Box Complex

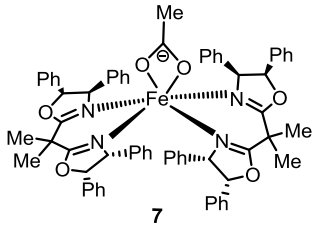
1.3.3.1 Results of TetraPy Box Ligand



L3

2,2-Bis-2-[4(R),5(S)-diphenyl-l,3-oxazolinyl]propane (**L3**): white solid (m.p. 153–154 °C); IR ν_{max} (neat)/cm^{-1}: 3056 (w), 1674 (s), 1450 (m), 1319 (m), 1140(s), 1119(m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.2–6.96(m, 10H), 5.98 (d, J = 10 Hz, 1H), 5.60 (d, 1H), 1.93 (s, 3H), 0.78 (d, *3*H), nearly identical to the literature data.[12]

1.3.3.2 Applications of Fe-TetraPh Box Complex

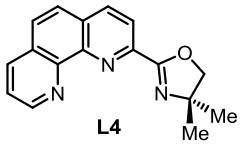


7

Complex **7** is effective to catalyze highly enantioselective intramolecular amino-hydroxylation of olefins with functionalized hydroxylamines as well as aminohydroxylation reaction for a variety of indoles.

1.3.4 Results of Fe-Phenanthroline Box Complex

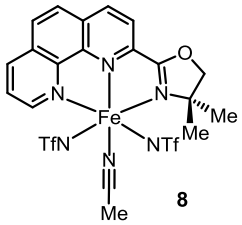
1.3.4.1 Results of Phenanthroline Box Ligand



L4

4,4-Dimethyl-2-(1,10-phenanthrolin-2-yl)-4,5-dihydrooxazole (**L4**): ligand **L4** was further purified by recrystallization from a hexanes/EtOAc mixture as a white solid (m.p. 106–108 °C). IR ν_{max} (neat)/cm^{-1}: 3385 (m), 3223 (m), 2966 (w), 1646 (s), 1493 (m), 1400 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.25 (dd, J = 4.3, 1.3 Hz, 1H), 8.43 (d, J = 8.3 Hz, 1H), 8.34 (d, J = 8.3 Hz, 1H), 8.29 (d, J = 6.9 Hz, 1H), 7.86 (q, J = 8.8 Hz, 2H), 7.68 (dd, J = 8.1, 4.4 Hz, 1H), 4.34 (s, 2H), 1.49 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.7, 150.4, 146.4, 145.9, 145.5, 136.6, 136.2, 129.4, 128.9, 128.0, 126.1, 123.4, 122.7, 79.8, 68.1, 28.5; HRMS (ESI, m/z): calcd for $C_{17}H_{16}N_3O^+$, [M + H^+]: 278.1288, found 278.1289.

1.3.4.2 Applications of Fe-Phenanthroline Box Complex



8

Complex **8** is effective to catalyze highly diastereo- and enantioselective intermolecular aminohydroxylation of olefin with a labile C-H bond as well as the allylic positon of substituted indole substrate.

1.4 CONCLUSIONS

We have successfully synthesized the iron(II) complexes [Fe(tetraMe–PyBox)$(OTf)_2$] (**3**), [Fe(tetraPh–PyBox)$(OTf)_2$] (**4**), [Fe(tetraPh–Box)$(OAc)_2$] (**7**) and [Fe(Phen–Box)$(NTf_2)_2$] (**8**) by the reaction of iron(II) salt with the corresponding N-based ligand. X-ray crystallographic analysis and reactivity studies of these iron complexes were performed. The results indicate that the reactivity of the iron complexes is dependent on their unique structures as well as the coordination abilities of N-based ligands to the iron center. Therefore, searching for new reactivity of those iron catalysts in the fields of total synthesis, new drug discovery, as well as novel reaction and methodology studies, show great importance.

2 CHAPTER II IRON(II)-CATALYZED AMINO-OXYGENATION OF ALKENES

2.1 INTRODUCTION

2.1.1 Naturally Occurring Molecules

Numerous biologically active alkaloids and pharmaceuticals contain chiral 1,2-amino alcohols, and as depicted in Figure **2**. However, the synthesis of 1,2-amino alcohol motifs is very challenging and synthetic approaches towards this important problem can be summarized in Figure **3**, including epoxide opening, nucleophilic substitution, imine reduction, aldehyde reduction, enamine oxidation, aziridine opening, etc.

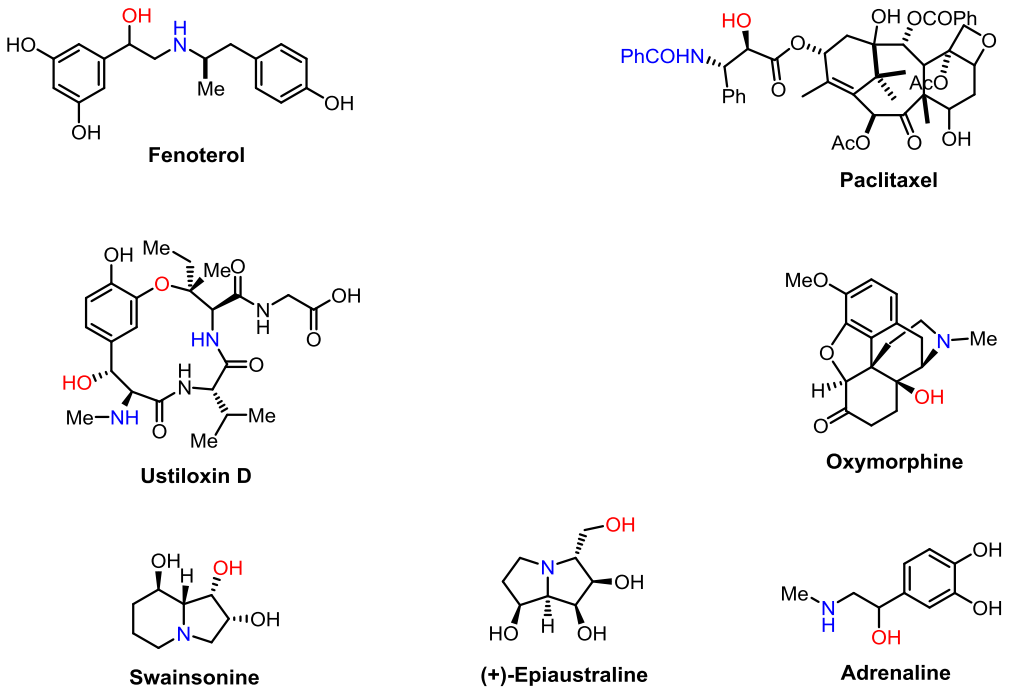


Figure 2. Compounds Containing the 1,2-Amino Alcohol Motifs

From Figure **3** we can see that, research into the simultaneous transfer of nitrogen and another heteroatom across a variety of double bonds by organocatalysis or metal catalyzed

methods show great advantages compared to other methods, because these catalytic reactions readily transform commodity chemicals to highly functionalized building blocks valuable to medicinal chemistry and pharmaceutical research.

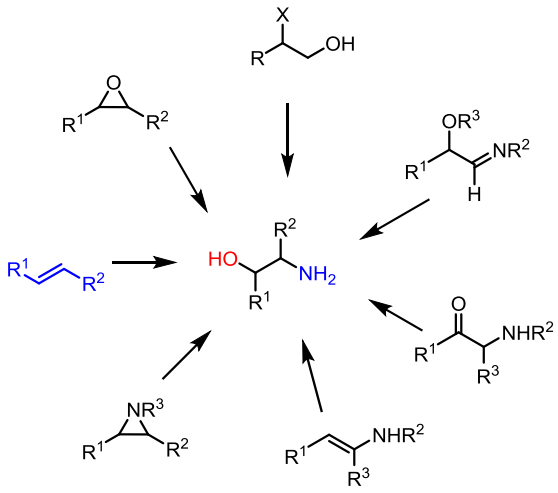
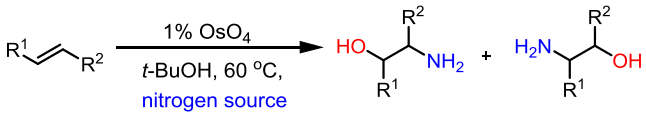


Figure 3. Approaches for the Synthesis of Vicinal 1,2-Amino Alcohols

We are interested in direct difunctionalization of alkenes with non-precious metal catalysts which is among the most utilized methods to introduce stereogenic nitrogen atoms in organic synthesis. The application of iron catalyst in organic synthesis is attractive for a few reasons.[14] First and foremost, iron is the most abundant metal in the earth; thus, the price of iron is much cheaper than other most often used precious metals. Secondly, considering the incorporation of iron compounds in biological systems during the evolutionary process, iron is crucial to many integral metabolic parts due to its relatively low toxicity. Last but not the least, from the research point of view, although the catalytic efficiency and applicability of iron is still behind palladium or some other metals in organic synthesis, publications related to iron in catalysis as well as organic synthesis has a tremendous increase just in the last few years, demonstrating the coming of the “iron age”.

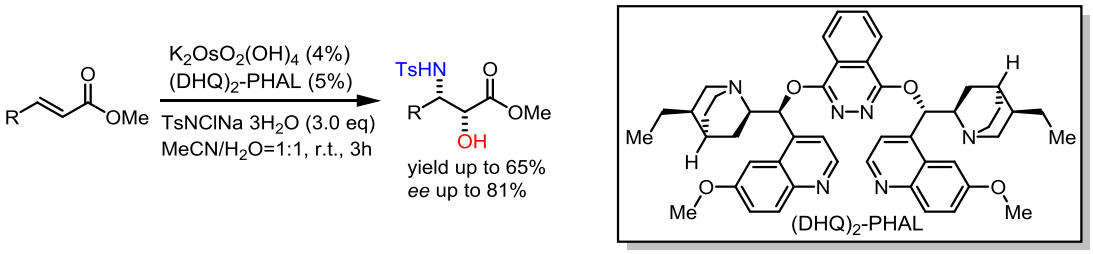
2.1.2 Osmium-Mediated Reactions

The pioneering asymmetric aminohydroxylation (AA) reported by K.B. Sharpless and coworkers in 1976 remains a powerful method for the synthesis of enantioenriched *syn*-vicinal amino alcohols.[15] Different from the well-known dihydroxylation reaction, the unsymmetrical addition brings the regioselectivity issue of the reaction affording two possible products, as illustrated in Scheme **8**. This osmium-catalyzed procedure provides the *cis* addition of the hydroxyl (OH) and arylsulfonamide ($ArSO_2NH_2$) moieties across an olefinic linkage with sixteen different olefin substrates, and yields ranging from 34% to 96%.[15b]



Scheme 8. Osmium-Catalyzed Sharpless Olefin AA

The asymmetric induction was first time achieved by using chiral tertiary amine ligands, which belongs to cinchona alkaloid family.[15a] In this case, chirality is transformed from a catalytic amount of osmium and an enantiopure ligand to chiral products in good yield and *ee*, as shown in Scheme **9**. The advantages of the AA are its simplicity, functional group tolerance as well as no requirement for auxiliary functional groups; however, certain barriers still exist such as the scope and utility of the reaction, which limits their applications.

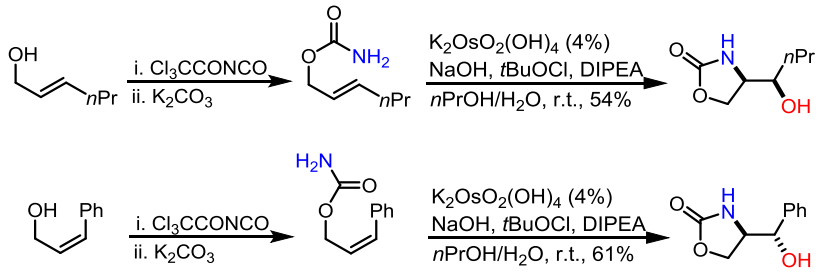


Scheme 9. Osmium-Catalyzed Enantioselective AA

Despite the advances achieved regarding control of the regio- and stereoselectivity in osmium-catalyzed aminohydroxylation, the reaction itself is still controlled by the substrates.

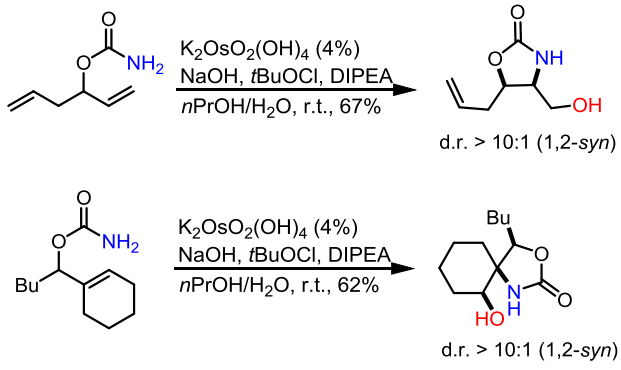
Donohoe[16] developed an Os-based tethered strategy to solve the regioselectivity problem in racemic olefin aminohydroxylation.

Starting from allylic alcohols, carbamate intermediates can be prepared in high yield by a two-step procedure, as shown in Scheme **10**. The reaction is stereospecific and proceeds with the only catalytic amount of catalyst loading with the application of the Sharpless AA conditions. A range of hydroxyl oxazolidinones with complete *syn* stereospecific the tethered osmium species across the alkene were thus achieved.[16f, 16h] Unfortunately, no *ee* was observed in the presence of $(DHQ)_2$-PHAL.



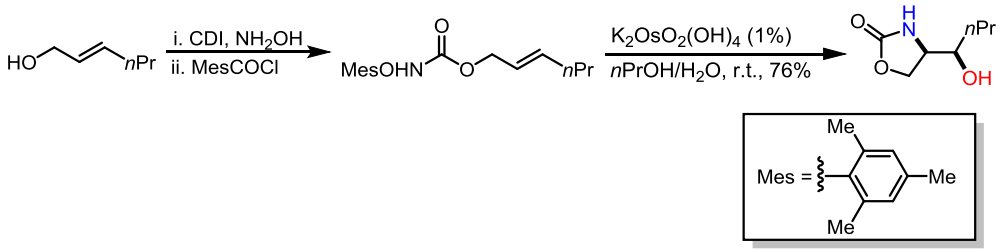
Scheme 10. Regioselective Aminohydroxylation of Allylic Carbamates

After illustrating achiral allyl carbamates with regio- and stereoselectivity, substrates bearing an allylic stereogenic center were further examined with the optimized reaction conditions, affording high *syn* diastereoselectivity showed in Scheme **11**.[16e, 16g]



Scheme 11. Regioselective Aminohydroxylation of Allylic Carbamates with Stereogenic Center

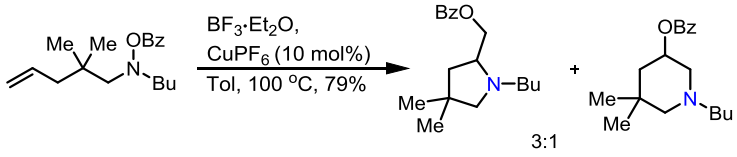
T o avoid the use of chlorinating agents, Donohoe and others discovered a replacement procedure for the synthesis of *N*-sulfonyloxy and *N*-carbonyloxy derivatives of a broad range of acyclic and cyclic allylic alcohols. The prepared intermediates can thus be converted to the corresponding hydroxyl oxazolidinones with higher yields as well as low catalyst loading.[16b-d]



Scheme 12. Improved Aminohydroxylation of Allylic Carbamates

2.1.3 Copper-Mediated Reactions

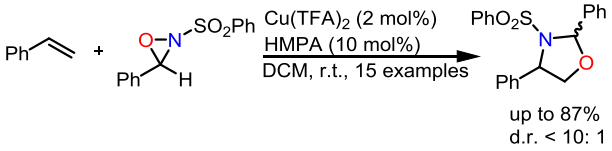
This reaction has also inspired extensive efforts to discover alternative approaches to address its inherent limitations. Göttlich[17] discovered the first radical aminohydroxylation of double bonds. *N*-benzoyl hydroxylamines are reduced by Cu(I) in the presence of a Lewis acid, followed by carbon radical oxidized by Cu(II) via a ligand transfer to furnish the cyclized products in moderate yields and different regioselectivity for pyrrolidines over piperidines. While the formation of piperidine goes through an unusual 6-*endo* radical cyclization, it might be caused by the *gem* dialkyl groups in the substrates.



Scheme 13. Copper(I)-Catalyzed Cyclization of Unsaturated *N*-Benzoyloxyamines

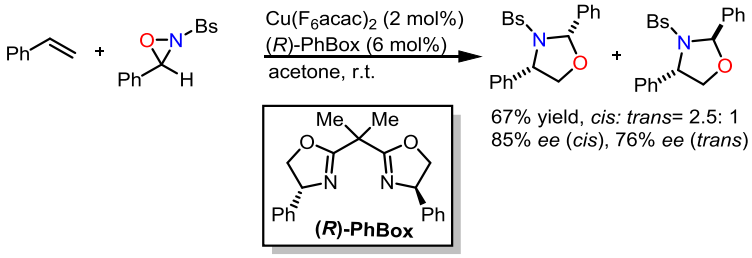
Yoon[18] firstly reported a novel copper(II)-catalyzed reaction of oxaziridines that affects regioselective aminohydroxylation of styrenes and electron-rich olefins in 2007, as shown in Scheme **14**.[18a] Cu(II) works as Lewis acid to activate the oxaziridine and nucleophilic attack by

styrenic olefins, allyl silanes, enol ethers as well as symmetrical dienes, subsequent ring closer onto the resultant benzylic cation to furnish highly chemoselective aminals. However, an extended reaction, limited substrates scope (only electron rich olefins that can sufficiently stabilize the carbon cation intermediate) and poor diastereoselectivity limited their further applications.



Scheme 14. Copper(II)-Catalyzed Aminohydroxylation of Styrenic Olefins

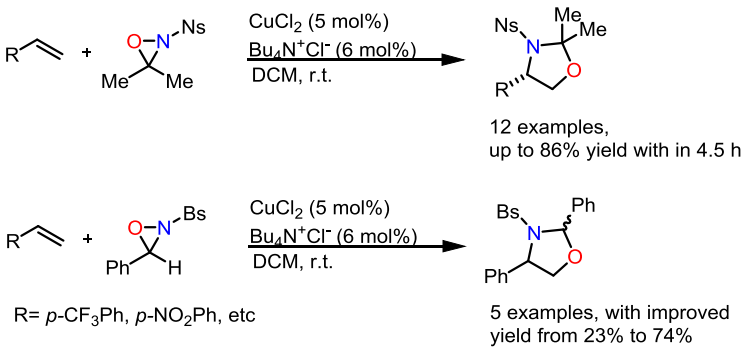
Subsequent reports have revealed this significant use of chiral bisoxazoline copper(II) complexes to provide good enantioselectivity for most electron rich styrenic olefins but low diastereoselectivity.[18d]



Scheme 15. Copper(II)-Catalyzed Enantioselective Aminohydroxylation

An important implement for this reaction is the discovery of dimethyloxaziridine with the combination of anionic halocuprate(II) complexes that takes care of the diastereoselectivity issue as well as reaction time problem for olefinic substrates as summarized in Scheme **16(a)**.[18c] In most cases, the reaction can finish within 4.5 h with improved yields, and the resulted products can be deprotected under milder conditions compared to the reduction conditions required for removal of an *N*-benzenesulfonyl group. Also, the anionic halocuprate(II) complexes show advantages over neutral copper(II) salts such as, dramatically increased amount of sterically and

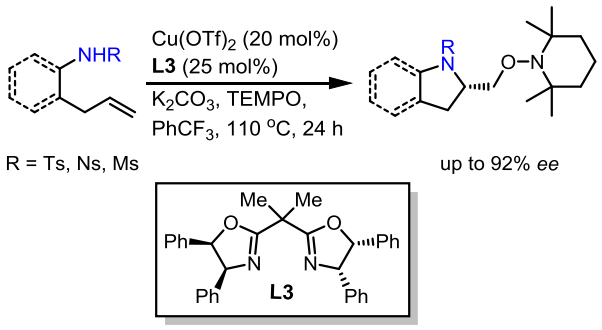
electronically deactivated styrenes, rate acceleration in most cases with dramatically enhanced yields indicated in Scheme **16(b)**.[18c]



Scheme 16. (a) New Oxaziridines-Mediated Aminohydroxylation

(b) Anionic Halocuprate(II) Complex as Enhanced Catalyst

Chemler[19] discovered copper can catalyze intramolecular olefin aminooxygenation in the presence of TEMPO, as depicted in Scheme **17**. This intramolecular process provides efficient access to a variety of chiral pyrrolidines and indolines of interest to synthetic organic and medicinal chemists.[19a] Although this methodology gives us another option for the preparation of the valuable vicinal amino alcohols directly from olefins, it is limited to terminal olefin systems. Besides that, further optimization of the reaction time and temperature is still needed in order to broaden its synthetic application.



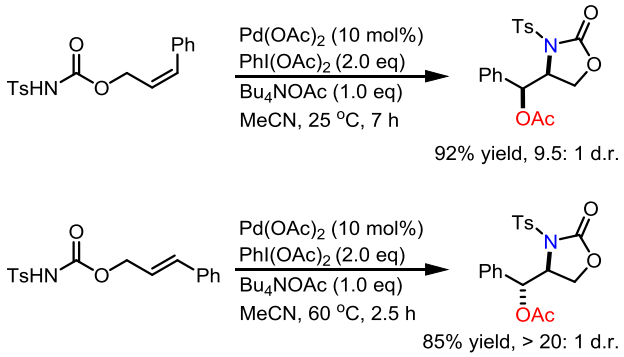
Scheme 17. Cu(II)-Catalyzed Enantioselective Intramolecular Aminooxygenation of Alkenes

2.1.4 Palladium-Mediated Reactions

Bäckvall[20] in 1975 reported the first direct aminooxygenation of the terminal and internal olefins catalyzed by a stoichiometric amount of Pd(II) catalyst. Alkene was initially activated by Pd(II) *via* nucleophilic attack to afford Pd(II) intermediate region isomers. The Pd-C bond was subsequently oxidized with $Pb(OAc)_2$ to generate vicinal amino motifs. Although highly diastereoselective *syn* addition products were afforded for symmetrically substituted internal olefins, only moderate regioselectivity can be achieved for terminal and asymmetrical alkenes.

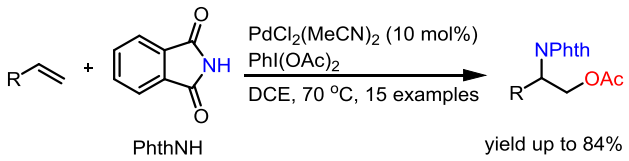
An investigation by Sorensen[21] in 2005 leads to a successful story of Pd(II)-catalyzed intramolecular oxyamination of olefins. A possible catalytic mechanism is that Pd(II) catalyzed reversible *trans*-amino metalation of the alkenes followed by generation of a protonated intermediate than can undergo an irreversible deprotonation process. Thus, the addition of base is crucial to the reaction rate and regioselectivity. After the alkyl Pd(II) intermediate being oxidized by $PhI(OAc)_2$, C-O will be forming through a reductive elimination process to complete the catalytic cycle.

In the same year, Peter Szolcsanyi described a novel method for the preparation of the 6-oxa-2-azabicyclo[3.2.1]octane skeleton featuring Pd(II)/$CuCl_2$-catalyzed N,O-bicyclization as a key step.[22]



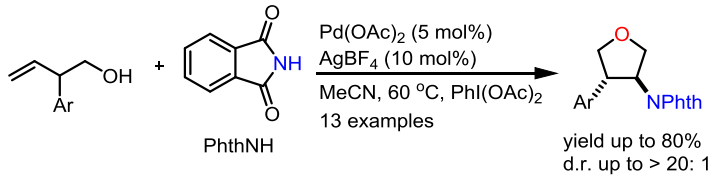
Scheme 18. Pd-Catalyzed Aminoacetoxylation of Alkenes

A significant development came in 2006, Stahl and Liu[23] demonstrated that simple Pd(II) complexes can catalyze intermolecular aminoacetoxylation of terminal alkenes, such as terminal allylic, homoallylic and enol ethers, with high levels of regio- and diastereoselectivity. However, excess alkene substrate was required to achieve high product yield.



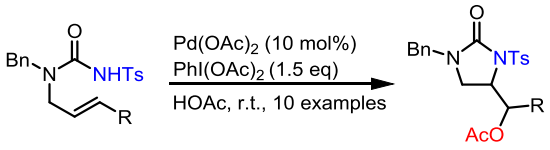
Scheme 19. Pd-Catalyzed Intermolecular Aminoacetoxylation of Alkenes

The following year, Sanford[24] enclosed that homoallylic alcohols could be cyclized to furnish 3-aminotetrahydrofurans in moderate to high diastereoselectivity. This process involves a Pd-catalyzed alkene aminopalladation to generate alkyl Pd species, followed by intramolecular oxidative functionalization and reductive elimination to afford stereoselectively tetrahydrofuran products.



Scheme 20. Pd-Catalyzed Formation of 3-Aminotetrahydrofuran Derivatives

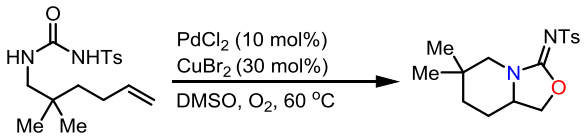
Recently, Bingfeng Shi[25] reported that a divergent synthesis of cyclic ureas and isoureas *via* a catalyst controlled aminoacetoxylation of alkenes with $PhI(OAc)_2$ as the oxidant in good yields under mild conditions.



Scheme 21. Pd-Catalyzed Aminoacetoxylation

2.1.5 Platinum-Mediated Reactions

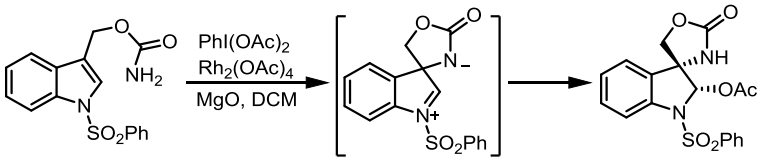
Kilian Muniz[26] disclosed that homogeneous Pt can catalyze 1,2 difunctionalizations of alkenes to deliver the corresponding bicyclic isoureas in high yields under aerobic conditions. More interestingly, the catalytic amount of Cu(II) oxidant is sufficient to turn over the reaction without any additives resulting in the formation of 5 or 6 member fused ring system with high chemoselectivity, and good diastereoselectivity in the presence of a stereocenter.



Scheme 22. Pt-Catalyzed Aerobic 1,2-Aminoacetoxylation of Alkenes

2.1.6 Rhodium-Mediated Reactions

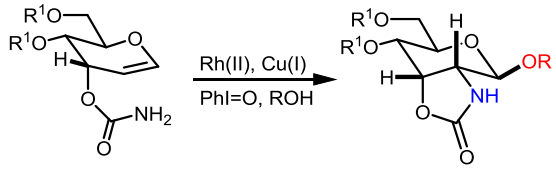
More recently, Albert Padwa[27] and co-work came up with the iodine (III)-mediated aziridination reaction of an indolyl-substituted carbamate which requires a Rh(II) catalyst and proceeds by metallonitrene intermediate. A metal-free zwitterion is generated by stepwise addition across the indole π-bond followed by Rh (II) detachment, which ultimately furnishes the final products, as demonstrated in Scheme **23**.



Scheme 23. Iodine(III)-Mediated Aziridination Reaction

Christian[28] subsequently came up with the amidoglycosylation reaction of allyl 3-carbamates catalyzed by rhodium and copper acyl nitrenoids in the presence of iodosobenzene. Glycal enol ether π-system will react with the metal nitrenoid leading to the formation of C2-N bond; sequential *β*-selective glycosylation may take place via a metal-complexed glycosyl

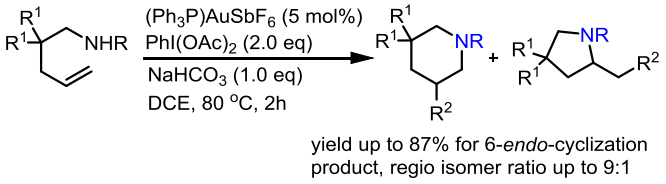
aziridine to afford highly diastereoselective glycosylation product without activation of Lewis acid.



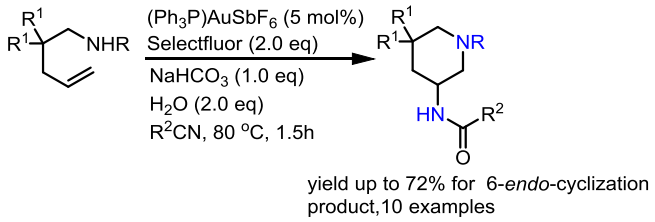
Scheme 24. Rh(II)-Catalyzed Amidoglycosylation

2.1.7 Gold-Mediated Reactions

The research group of Cristina Nevado[29] reported the first gold-catalyzed amino-oxygenation and aminoamidation of unactivated alkenes. The afforded results are complementary to *5-exo* palladium-catalyzed process but with expanded substrates scope compared to that of copper-mediated reactions. Au(I) can activate the alkene and favor the 6-*endo* nitrogen cyclization fashion to form the carbon Au(III) intermediate in a reversible manner. Due to the highly electrophilic nature of the Au(III), varying levels of nucleophiles, such as water, alcohol, even acetonitrile can be employed in the ligand exchange process, thus the reductive elimination will subsequently occur to afford highly diastereoselective desired products.



Scheme 25. Gold-Catalyzed Aminooxygenation Reaction of Alkenes

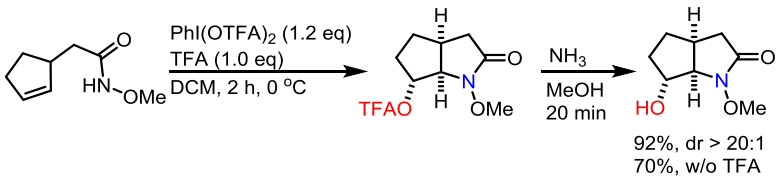


Scheme 26. Gold-Catalyzed Aminoamidation Reaction of Alkenes

2.1.8 Hypervalent Iodine-Mediated Reactions

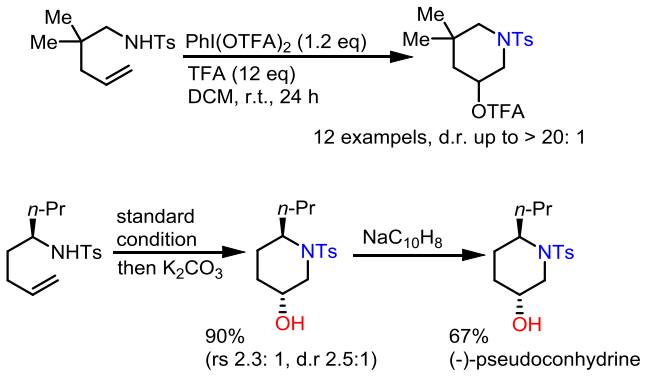
K. C. Nicolaou, P. S. Baran and others discovered and subsequently developed a novel cyclization reaction of *N*-aryl amides (anilides) onto internally located unactivated olefins to form heterocycles induced by the *o*-iodoxybenzoic acid (IBX).[30] It has a great success for the synthesis of lactams, cyclic urethanes, hydroxyl amines, amino sugars, *et al*. Mechanistic investigations indicated that an SET (single electron transfer) from the anilide functionality to IBX followed by a radical trapping process. The simplicity in terms of operation and substrates preparation make this a great method for constructing small molecule libraries for biological and pharmaceutical applications.

In the year 2009, Duncan J. Wardrop[31] and coworkers showed that when unsaturated *o*-alkyl hydroxamates were treated with phenyliodine(III) bis(trifluoroacetate) (PIFA) in pure DCM at 0 °C, it subsequently underwent an intramolecular cyclization to afford the *anti* addition products in high yield and excellent diastereoselectivity. This alkene oxamidation method represents a remarkable method for rapid construction of these pharmaceutically important *N*-heterocycles.



Scheme 27. Intramolecular Oxamidation of Unsaturated O-Alkyl Hydroxamates

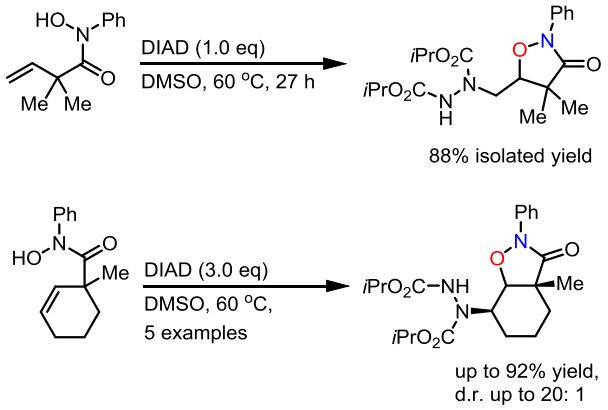
Different from metal or Lewis acid catalyzed reactions, Forrest E. Michael[32] have developed a broadly applicable, high yielding oxyamination reaction promoted by a Brønsted acid with high regioselectivity and excellent diastereoselectivity. The oxidant loading is decreased without diminished yield for *endo* cyclization products, and a reaction condition is much milder in terms of temperature although with extended reaction time. The showcase total synthesis of (-)-Pseudoconhydrine is very concise and interesting.



Scheme 28. Metal-Free Aminotrifluoroacetoxylation of Alkenes

2.1.9 Hydroxamic Acids-Mediated Reactions

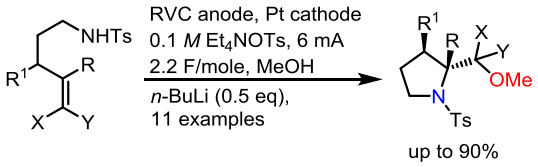
A significant improved to metal-free alkene oxyamination is described by Erik Alexanian[33] in 2011. This radical-mediated process capitalizes on the unique feature of aminoxyl radical in difunctionalizing alkenes using diisopropyl azodicarboxylate (DIAD) as a simple radical trap. The furnished high levels of diastereoselective *syn* cyclic oxyamination products are complementary to the previously reported *cis*-selective process but with single regioisomers. Initial extensions of the radical mediated difunctionalization to multibond-forming cascade processes are also described. Future work will be focused on applications in complex molecule synthesis.



Scheme 29. Metal-Free Oxyaminations of Alkenes Using Hydroxamic Acids

2.1.10 Electrochemical Approach

Moeller et al.[34] published an electrochemical approach for the synthesis of proline derivatives by oxidative anodic cyclization reactions bearing electron-rich alkenes, as demonstrated in Scheme **30**. The reactions benefit from the use of a less polar radical cation intermediate and the use of more basic reaction conditions, which is complementing to previously reported iodine protocols. However, the diastereoselectivity, in this case, is controlled by the substrates.

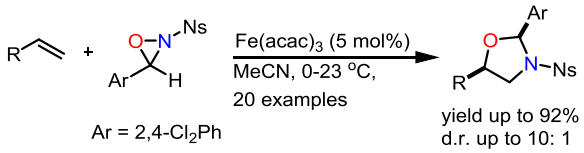


Scheme 30. Intramolecular Anodic Olefin Coupling Reaction

2.1.11 Iron-Mediated Reactions

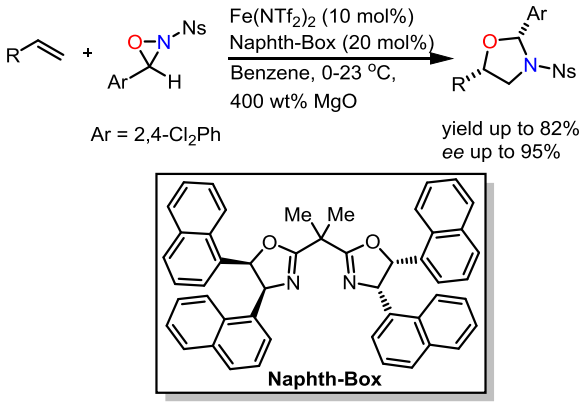
Despite these important achievements above, the direct conversion of a *trans*-olefin to a 1,2 *anti*-amino alcohol remains as an unsolved synthetic problem. In addition, the iron-catalyzed aminohydroxylation is a less-explored process. In the year 2010, Yoon[35] and others established a Fe(III)-catalyzed intermolecular aminohydroxylation of a variety of olefins, such as styrenic

olefins, dienes as well as aliphatic olefins, with *N*-sulfonyl oxaziridine as the N-O sources. More interestingly, the afforded product with an amino group on the terminal carbon, this regioselectivity is complementary to that observed with their reported Cu(II)-mediated reactions, wherein the amino-functional group in at the internal position. Although the mechanism of this novel reaction was unclear at that time, this unusual phenomenon indicates the different reaction pathway compared to that of the Cu(II)-catalyzed reaction. It turns out to be a useful synthetic strategy for the synthesis of 1,2-aminoalcohols.



Scheme 31. Iron-Catalyzed Aminohydroxylation of Olefins with *N*-Sulfonyl Oxaziridines

In a more recent publication, Yoon's group discovered that a novel iron(II) bis(oxazoline) complex is capable of catalyzing regioselective and enantioselective oxyamination of alkenes with *N*-sulfonyl oxaziridines.[36] On one hand, this process furnishes highly enantioenriched and synthetically useful 1,2-amino alcohol precursors. On the other hand, the regioselectivity of this reaction is also complementary to that obtained from the copper(II)-catalyzed reaction. Thus, this method capitalizes on the regio- and stereochemical control of 1,2-amino alcohol motifs.



Scheme 32. Iron-Catalyzed Asymmetric Oxyamination of Olefins

2.1.12 Expected Results

Our group at Georgia State University, we are interested in discovering new iron-catalyzed olefin amination methods that are unique in organic synthesis, pharmaceutical application, and biomedical engineering. Herein, we describe an iron(II)-catalyzed diastereoselective aminohydroxylation of an olefin to afford a 1,2 *anti*-amino alcohol with a functionalized hydroxylamine, possibly *via* an iron nitrenoid[37] intermediate. The catalysts are able to transfer both the *N* and *O* groups of the hydroxylamine intramolecularly to a variety of olefins, affording amino alcohols with a stereochemical array that is difficult to access with other known methods. We envision this discovery offers an appealing alternative for existing aminohydroxylation methods.

2.2 EXPERIMENT

2.2.1 General Procedures

General procedures. All reactions were performed in oven-dried or flame-dried round-bottom flasks and vials. Stainless steel syringes and cannula were used to transfer air- and moisture-sensitive liquids. Flash chromatography was performed using silica gel 60 (230-400 mesh) from Sigma–Aldrich.

Materials. Commercial reagents were purchased from Sigma-Aldrich, Fluka, EM Science, and Lancaster and used as received. All solvents were used after being freshly distilled unless otherwise noted.

Instrumentation. Proton nuclear magnetic resonance (^{1}H NMR) spectra， carbon nuclear magnetic resonance (^{13}C NMR) spectra and fluorine nuclear magnetic resonance (^{19}F NMR) were recorded on Bruker UltraShield-400 (400 MHz). Chemical shifts for protons are

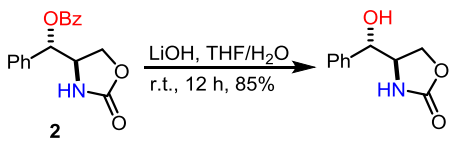
reported in parts per million downfield from tetramethylsilane and are referenced to the NMR solvent residual peak ($CHCl_3$: δ 7.26). Chemical shifts for carbons are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$: δ 77.0). Chemical shifts for fluorine are reported in parts per million downfield and are referenced to the fluorine resonances of $CFCl_3$. Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz), and integration.

The mass spectroscopic data were obtained at the Georgia State University mass spectrometry facility using a Micromass Platform II single quadruple instrument. Infrared (IR) spectra were obtained using a Perkin Elmer Spectrum 100 FT-IR spectrometer. Data are represented as follows: frequency of absorption (cm^{-1}) and absorption strength (s = strong, m = medium, w = weak).

Abbreviations used: EtOH–ethanol, EtOAc–ethyl acetate, THF–tetrahydrofuran, MeOH–methanol, Et2O–diethyl ether, CH_2Cl_2–dichloromethane, TEA–triethylamine, MeCN–acetonitrile, MS–molecular sieves, CDI–1,1′-carbonyldiimidazole, Troc–2,2,2-trichloroethoxycarbonyl, DCC–N,N′-dicyclohexylcarbodiimide, TLC–thin layer chromatography ，Boc_2O–di-tert-butyl dicarbonate, DMAP−4-dimethylaminopyridine.

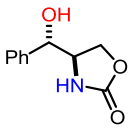
2.2.2 Relative Stereochemistry Determination of the Product

2 was hydrolyzed and compared with reported literature data.[16h, 38]

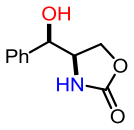


Scheme 33. Hydrolysis of Oxazolidone

Comparison of ^{1}H NMR data of hydrolysis product of **2** with ones of known compounds:



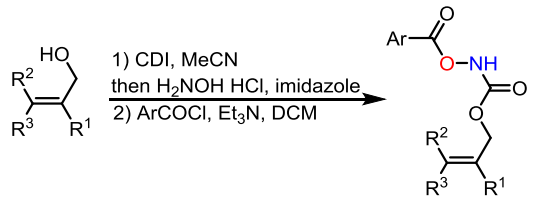
S1



S2

^{1}H NMR of **S1**	^{1}H NMR of **S2**	^{1}H NMR of hydrolysis products of **2**
7.28-7.54 (5H, m), 4.97 (1H, brs), 4.69 (1H, d, *J* = 6.0 Hz), 4.44-4.52 (2H, m), 3.98-4.03 (1H, m), 2.47 (1H, br, s)	7.32-7.44 (5H, m), 5.54 (1H, br, s), 4.63 (1H, dd, *J* = 7.5, 3.5 Hz), 4.23 (1H, t, *J* = 9.0 Hz), 4.12 (1H, dd, *J* = 9.0, 5.5 Hz), 4.05 (1H, m), 2.48 (1H, d, *J* = 3.5 Hz)	7.30-7.53 (5H, m), 5.09 (1H, brs), 4.69 (1H, d, *J* = 6.4 Hz), 4.42-4.51 (2H, m), 3.98-4.03 (1H, m)

2.2.3 Synthesis and Characterization of Olefin Substrates

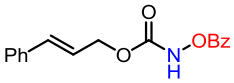


Scheme 34. Substrates Preparation

1,1'-Carbonyldiimidazole (CDI, 1.5 equiv) was added to a solution of alcohol (1.0 equiv) in acetonitrile (0.2 M) and stirred at room temperature. The reaction was monitored by TLC, and upon its completion, imidazole (4.0 equiv) and hydroxylamine hydrochloride (5.0 equiv) were added and stirring continued until TLC analysis indicated the reaction reached completion. After removing the solvent, the residue was partitioned between ethyl acetate and 1 M HCl followed by extraction of the aqueous phase with ethyl acetate. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated in *vacuo* to afford the crude hydroxyl carbamate

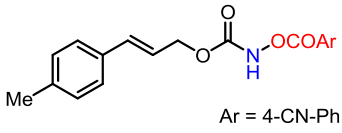
product, which was purified by flash column chromatography with 40 % ethyl acetate-hexane (63-91 % yield). A 25 mL flame-dried round bottom flask was charged with a stirring bar, hydroxyl carbamate (1.0 equiv), NEt_3 (1.1 equiv) and diethyl ether (0.2 M). After stirring at 0 °C for 5 mins, ArCOCl (1.1 equiv) was added dropwise over 10 min. The mixture was stirred for 2-4 hrs until TLC analysis indicates full conversion of the starting material. The mixture was then cooled to 0 °C and cold water was added to quench the reaction. The aqueous layer was extracted with ethyl acetate for three times. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated in *vacuo* to afford the crude product, which was purified by flash column chromatography using 20 % ethyl acetate-hexane (78-98 % yield).

Allylic alcohol substrates in Table **8** were prepared according to literature methods.[39]



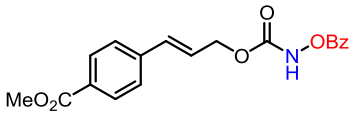
S3-1

Cinnamyl benzoyloxycarbamate (**S3-1**): White solid, mp: 95-97 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.40 (1H, s), 8.13 (2H, d, J = 8.4 Hz), 7.69-7.65 (1H, m), 7.53-7.50 (2H, m), 7.42-7.28 (5H, m), 6.72 (1H, d, J = 16.0 Hz), 6.33 (1H, dt, J = 16.0, 6.4 Hz), 4.90 (1H, d, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 165.9, 165.5, 136.0, 135.0, 134.3, 130.0, 128.7, 128.6, 128.3, 126.8, 126.7, 122.3, 67.3; IR (film) ν_{max}, 3242 (m), 1770 (s), 1759 (s), 1731 (s), 1600 (m), 1490 (s), 1451 (s), 1389 (s), 1179 (m), 1108 (s), 1038 (m), 1004 (m), 967 (m), 854(m), 749 (s), 705 (s), 694 (s) cm^{-1}; HRMS (ESI-TOF) for $C_{17}H_{14}NO_4$ [M-H$^+$] calcd 296.0923, found 296.0933.



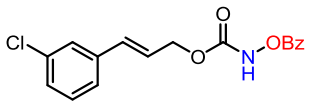
S3-2

(*E*)-3-(p-tolyl)allyl (4-cyanobenzoyl)oxycarbamate (**S3-2**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.46 (1H, s), 8.22 (2H, d, *J* = 8.0 Hz), 7.81 (2H, d, *J* = 8.0 Hz), 7.30 (2H, d, *J* = 7.6 Hz), 7.16 (2H, d, *J* = 7.2 Hz), 6.68 (1H, d, *J* = 15.6 Hz), 6.25 (1H, dt, *J* = 16.0, 6.4 Hz), 4.89 (1H, d, *J* = 6.4 Hz); ^{13}C NMR (CDCl3, 100 MHz): δ ppm 164.3, 156.1, 138.4, 135.5, 133.1, 132.5, 130.6, 130.5, 129.4, 129.2, 126.7, 120.8, 117.7, 117.6, 67.8, 21.3; IR (film) ν_{max}, 3235 (w), 1772 (s), 1732 (w), 1717 (s), 1491 (m), 1234 (s), 1118 (s), 1108 (s), 1040 (m), 1005 (m), 970 (m), 765 (m), 706 (s) cm^{-1}; HRMS (ESI-TOF) for $C_{19}H_{15}N_2O_4$ [M-H$^+$] calcd 335.1032, found 335.1032.



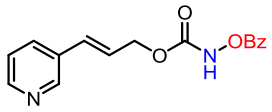
S3-3

(*E*)-Methyl 4-(3-(((benzoyloxy)carbamoyl)oxy)prop-1-en-1-yl)benzoate (**S3-3**): White solid, mp: 109-111 $^{\circ}$C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.50 (1H, s), 8.01 (2H, d, *J* = 8.0 Hz), 7.67 (2H, d, *J* = 7.6 Hz), 7.66 (1H, t, *J* = 7.6 Hz), 7.52 (2H, t, *J* = 7.6 Hz), 7.44 (2H, d, *J* = 8.0 Hz), 6.73 (1H, d, *J* = 16.0 Hz), 6.41 (1H, dt, *J* = 16.0, 6.0 Hz), 4.92 (1H, d, *J* = 6.0 Hz), 3.93 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 166.8, 165.8, 156.3, 140.4, 134.3, 133.5, 129.99, 129.96, 129.6, 128.8, 126.6, 126.3, 125.0, 66.8, 52.1; IR (film) ν_{max}, 3248 (w), 2953 (w), 1716 (m), 1606 (m), 1452 (m), 1436 (m), 1278 (s), 1179 (s), 1106 (s), 1041 (m), 1005 (m), 970 (m), 960 (m), 866 (m), 763 (s), 706 (s) cm^{-1}; HRMS (ESI-TOF) for $C_{19}H_{16}NO_6$ [M-H$^+$] calcd 354.0978, found 354.0967.



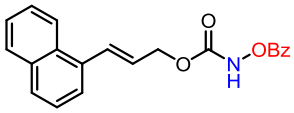
S3-4

(*E*)-3-(3-Chlorophenyl)allyl benzoyloxycarbamate (**S3-4**): White solid, mp: 101-103 $^{\circ}$C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.46 (1H, s), 8.13 (2H, d, J = 8.0 Hz), 7.67 (1H, t, J = 7.6 Hz), 7.51 (2H, t, J = 7.6 Hz), 7.38 (1H, s), 7.28-7.26 (3H, m), 6.64 (1H, d, J = 16.0 Hz), 6.31 (1H, dt, J = 16.0, 6.0 Hz), 4.89 (2H, d, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 165.8, 156.3, 137.9, 134.6, 134.3, 133.2, 130.0, 129.8, 128.7, 128.2, 126.7, 124.9, 123.9, 66.8; IR (film) ν_{max}, 3272 (w), 1733 (s), 1599 (m), 1566 (m), 1452 (s), 1318 (m), 1224 (s), 1179 (m), 1094 (s), 1004 (s), 964 (s), 885 (m), 765 (s), 682 (s) cm^{-1}; HRMS (ESI-TOF) for $C_{17}H_{13}NO_4Cl$ [M-H$^+$] calcd 330.0533, found 330.0533.



S3-5

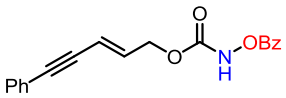
(*E*)-3-(Pyridin-4-yl)allyl benzoyloxycarbamate (**S3-5**): White solid, mp: 105-107 $^{\circ}$C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.37 (1H, s), 8.57 (1H, s), 8.12 (2H, d, J = 8.0 Hz), 7.71 (1H, d, J = 8.0 Hz), 7.65 (1H, t, J = 7.6 Hz), 7.50 (2H, t, J = 7.6 Hz), 7.28 (1H, s), 6.67 (1H, d, J = 16.0 Hz), 6.37 (1H, dt, J = 16.0, 6.0 Hz), 4.89 (2H, d, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 165.8, 156.4, 148.9, 148.3, 134.2, 133.2, 130.6, 130.0, 128.7, 126.8, 125.0, 124.0, 66.4; IR (film) ν_{max}, 2924 (w), 1745 (s), 1636 (w), 1452 (m), 1363 (w), 1280 (s), 1113 (s), 902 (w), 750 (m), 706 (m) cm^{-1}; HRMS (ESI-TOF) for $C_{16}H_{13}N_2O_4$ [M-H$^+$] calcd 297.0875, found 297.0871.



S3-6

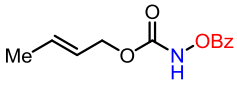
(*E*)-3-(Naphthalen-1-yl)allyl benzoyloxycarbamate (**S3-6**): White solid, mp: 75-77 $^{\circ}$C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.41 (1H, s), 8.18-8.10 (3H, m), 7.88 (1H, d, J = 8.8 Hz),

7.83 (1H, d, *J* = 8.4 Hz), 7.67 (1H, t, *J* = 7.2 Hz), 7.62 (1H, d, *J* = 7.2 Hz), 7.54-7.47 (6H, m), 6.36 (1H, dt, *J* = 16.0, 6.0 Hz), 5.02 (2H, d, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 165.9, 156.5, 134.3, 133.8, 133.6, 132.1, 131.1, 130.0, 128.8, 128.6, 126.7, 126.3, 125.9, 125.6, 125.5, 124.2, 123.7, 67.3; IR (film) ν_{max}, 3268 (w), 1744 (s), 1601 (m), 1452 (m), 1396 (m), 1319 (m), 1223 (s), 1179 (m), 1108 (m), 1040 (m), 1004 (m), 969 (m), 765 (s), 750 (s) cm^{-1}; HRMS (ESI-TOF) for $C_{21}H_{16}NO_4$ [M-H$^+$] calcd 347.1158, found 347.1155.



S3-7

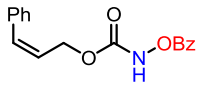
(*E*)-5-Phenylpent-2-en-4-yn-1-yl benzoyloxycarbamate (**S3-7**): Yellow solid, mp: 62-64 ºC, ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.83 (1H, s), 8.12 (2H, d, *J* = 7.2 Hz), 7.62 (1H, t, *J* = 7.6 Hz), 7.49-7.45 (4H, m), 7.34-7.32 (3H, m), 6.27 (1H, dt, *J* = 16.0, 6.0 Hz), 6.03 (1H, d, *J* = 16.0 Hz), 4.81 (2H, d, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 165.8, 156.4, 135.4, 134.3, 131.6, 130.0, 128.8, 128.5, 128.4, 126.7, 123.0, 114.3, 91.4, 86.8, 66.1; IR (film) ν_{max}, 3254 (m), 1747 (s), 1489 (m), 1452 (m), 1228 (s), 1179 (m), 1112 (s), 1004 (m), 952 (m), 756 (s), 706 (m) cm^{-1}; HRMS (ESI-TOF) for $C_{19}H_{15}NO_4Na$ [M+Na$^+$] calcd 344.0899, found 344.0912.



S3-8

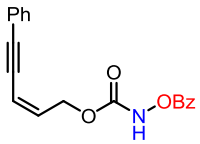
(*E*)-But-2-en-1-yl benzoyloxycarbamate (**S3-8**): White solid, mp: 65-67 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.64 (1H, s), 8.08 (2H, d, *J* = 7.6 Hz), 7.62 (1H, t, *J* = 7.6 Hz), 7.46 (1H, d, *J* = 7.6 Hz), 5.87-5.78 (1H, m), 5.63-5.56 (1H, m), 4.63 (2H, d, *J* = 6.4 Hz), 1.71 (3H, d, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 165.8, 156.6, 134.2, 132.4, 130.0, 128.7, 126.8, 124.4, 67.4, 17.8; IR (film) ν_{max}, 3273 (w), 2969 (w), 1733 (s), 1601 (w), 1451 (m), 1319

(w), 1275 (m), 1259 (m), 1225 (s), 1178 (m), 1104 (m), 966 (m), 750 (s), 704 (m) cm^{-1}; HRMS (ESI-TOF) for $C_{12}H_{12}NO_4$ [M-H^+] calcd 234.0766, found 234.0775.



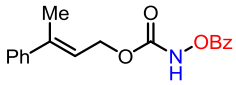
S3-9

(*Z*)-3-Phenylallyl benzoyloxycarbamate (**S3-9**): Colorless oil, ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.52 (1H, s), 8.12 (2H, d, *J* = 7.6 Hz), 7.66 (1H, t, *J* = 7.4 Hz), 7.51 (2H, t, *J* = 7.6 Hz), 7.37 (2H, t, *J* = 7.6 Hz), 7.30 (1H, t, *J* = 7.8 Hz), 7.24 (2H, d, *J* = 7.4 Hz), 6.73 (1H, d, *J* = 7.6 Hz), 5.90-5.83 (1H, m), 5.01 (2H, d, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 165.9, 165.5, 135.8, 134.3, 133.9, 130.0, 128.7, 128.5, 127.7, 126.7, 124.9, 63.6; IR (film) ν_{max}, 3267 (m), 1734 (s), 1600 (m), 1451 (m), 1318 (m), 1227 (s), 1119 (m), 1107 (s), 1040 (m), 1004 (m), 855 (m), 765 (m), 701 (s) cm^{-1}; HRMS (ESI-TOF) for $C_{17}H_{16}NO_4$ [M+H^+] calcd 298.1079, found 298.1065.



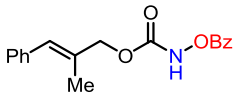
S3-10

(*Z*)-5-Phenylpent-2-en-4-yn-1-yl benzoyloxycarbamate (**S3-10**): Yellow solid, mp: 45-47 º C, ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.55 (1H, s), 8.11 (2H, d, *J* = 7.6 Hz), 7.65 (1H, t, *J* = 7.6 Hz), 7.52-7.46 (4H, m), 7.35-7.33 (3H, m), 6.10 (1H, dt, *J* = 11.2, 6.0 Hz), 5.95 (1H, d, *J* = 11.2 Hz), 5.10 (2H, d, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 165.8, 156.4, 135.0, 134.3, 131.6, 130.0, 128.73, 128.66, 128.4, 126.7, 122.8, 113.7, 96.5, 84.3, 64.4; IR (film) ν_{max}, 3266 (m), 1747 (s), 1490 (m), 1452 (m), 1230 (s), 1180 (m), 1110 (s), 1040 (m), 756 (s), 706 (m) cm^{-1}; HRMS (ESI-TOF) for $C_{19}H_{15}NO_4Na$ [M+Na^+] calcd 344.0899, found 344.0912.



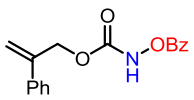
S3-11

(*E*)-3-Phenylbut-2-en-1-yl benzoyloxycarbamate (**S3-11**): White solid, mp: 64-66 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.72 (1H, s), 8.13 (2H, d, J = 7.6 Hz), 7.64 (1H, t, J = 7.6 Hz), 7.51-7.31 (7H, m), 5.95 (1H, t, J = 7.2 Hz), 4.97 (2H, d, J = 6.8 Hz), 2.14 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 165.9, 156.8, 142.4, 141.3, 134.2, 130.0, 128.7, 128.4, 127.7, 126.8, 125.9, 120.5, 63.9, 16.3; IR (film) ν_{max}, 3274 (w), 1733 (s), 1600 (m), 1451 (s), 1346 (m), 1317 (m), 1225 (s), 1179 (m), 1104 (m), 1039 (m), 1004 (m), 931 (m), 854 (m), 751 (s), 697 (s) cm^{-1}; HRMS (ESI-TOF) for $C_{18}H_{16}NO_4$ [M-H$^+$] calcd 310.1079, found 310.1087.



S3-12

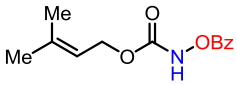
(*E*)-2-Methyl-3-phenylallyl benzoyloxycarbamate (**S3-12**): White solid, mp: 85-87 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.66 (1H, brs), 8.13 (2H, d, J = 7.6 Hz), 7.65 (1H, t, J = 6.8 Hz), 7.50 (2H, t, J = 6.8 Hz), 7.38-7.25 (5H, m), 6.59 (1H, s), 4.82 (2H, s), 1.93 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 165.9, 156.7, 136.8, 134.3, 132.0, 130.0, 129.0, 128.8, 128.2, 126.9, 126.7, 72.3, 15.4; IR (film) ν_{max}, 3274 (w), 2990 (w), 1744 (m), 1600 (m), 1452 (m), 1320 (m), 1275 (s), 1260 (s), 1228 (s), 1107 (m), 1004 (m), 856 (m), 750 (s), 700 (m) cm^{-1}; HRMS (ESI-TOF) for $C_{18}H_{16}NO_4$ [M-H$^+$] calcd 310.1079, found 310.1087.



S3-13

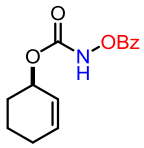
Methyl 4-((((((2-phenylallyl)oxy)carbonyl)amino)oxy)carbonyl)benzoate (**S3-13**): White solid, mp: 75-77 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.45 (1H, s), 8.14-8.11 (4H, m),

7.44-7.42 (2H, m), 7.37-7.30 (3H, m), 5.60 (1H, s), 5.43 (1H, d, J = 0.8 Hz), 5.15 (2H, d, J = 0.4 Hz), 3.98 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 166.0, 165.0, 156.1, 141.8, 137.6, 135.0, 130.3, 129.9, 129.8, 128.5, 128.2, 126.0, 116.1, 68.0, 52.6; IR (film) ν_{max}, 3267 (w), 1738 (s), 1600 (m), 1452 (m), 1318 (m), 1225 (s), 1179 (m), 1095 (m), 1044 (m), 1003 (m), 915 (m), 855 (m), 828 (w), 764 (s) cm^{-1}; IR (film) ν_{max}, 3261 (w), 3005 (w), 1722 (s), 1575 (w), 1436 (m), 1409 (m), 1276 (s), 1261 (s), 1223 (s), 1102 (m), 1009 (m), 872 (m), 750 (s), 723 (m) cm^{-1}; HRMS (ESI-TOF) for $C_{19}H_{18}NO_6$ [M-H$^+$] calcd 354.1056, found 354.1047.



S3-14

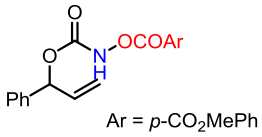
Methyl 4-(((5-methylhex-4-enamido)oxy)carbonyl)benzoate (**S3-14**): White solid, mp: 92-94 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.13-8.08 (4H, m), 5.13 (1H, s), 3.96 (3H, s), 2.38 (4H, s), 1.70 (3H, s), 1.63 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 166.0, 164.0, 134.9, 134.0, 130.4, 129.9, 129.7, 122.0, 52.6, 33.2, 25.7, 23.6, 17.7; IR (film) ν_{max}, 3211 (w), 2918 (w), 1781 (s), 1729 (s), 1671 (s), 1435 (m), 1280 (s), 1234 (s), 1106 (s), 1073 (m), 1017 (m), 750 (m), 721 (m) cm^{-1}; HRMS (ESI-TOF) for $C_{16}H_{20}NO_5$ [M+H$^+$] calcd 306.1341, found 306.1348.



S3-15

Cyclohex-2-en-1-yl benzoyloxycarbamate (**S3-15**): White solid, mp: 63-65 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.43 (1H, s), 8.10 (2H, d, J = 8.0 Hz), 7.64 (1H, t, J = 7.6 Hz), 7.49 (2H, t, J = 7.6 Hz), 6.02-5.97 (1H, m), 5.79-5.77 (1H, m), 5.32-5.31 (1H, m), 2.08-1.84 (4H, m), 1.77-1.63 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 165.9, 156.4, 134.2, 133.6,130.0, 128.7, 126.8, 124.9, 71.0, 28.2, 24.8, 18.6; IR (film) ν_{max}, 3275 (w), 2942 (w), 1733 (s), 1601 (w), 1452

(m), 1229 (s), 1179 (m), 1106 (s), 1040 (m), 1003 (m), 909 (m), 750 (m), 706 (m) cm^{-1}; HRMS (ESI-TOF) for $C_{14}H_{16}NO_4$ [$M+H^+$] calcd 262.1079, found 262.1085.



S3-16

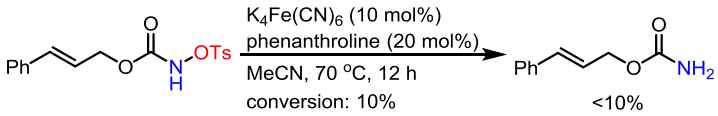
Methyl 4-((((((1-phenylallyl)oxy)carbonyl)amino)oxy)carbonyl)benzoate (**S3-16**): White solid, mp: 39-41 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.86 (1H, s), 8.11 (4H, s), 7.35-7.28 (5H, m), 6.29 (1H, d, J = 6.0 Hz), 6.08-5.99 (1H, m), 5.39-5.28 (2H, m), 3.95 (3H, s); ^{13}C NMR(CDCl3, 100 MHz): δ ppm 166.0, 165.0, 164.9, 155.7, 137.9, 135.4, 134.9, 130.5, 129.9, 129.8, 128.6, 128.5, 127.1, 117.8, 78.9, 52.6; IR (film) ν_{max}, 3266 (w), 2942 (w), 1725 (s), 1436 (m), 1287 (s), 1270 (m), 1105 (s), 1040 (m), 1003 (m), 909 (m), 725 (m), 700 (m) cm^{-1}; HRMS (ESI-TOF) for $C_{19}H_{18}NO_6$ [$M+H^+$] calcd 356.1134, found 356.1123.

2.2.4 Procedure for Iron(II)-Catalyzed Olefin Aminohydroxylation

2.2.4.1 Substrates Screen

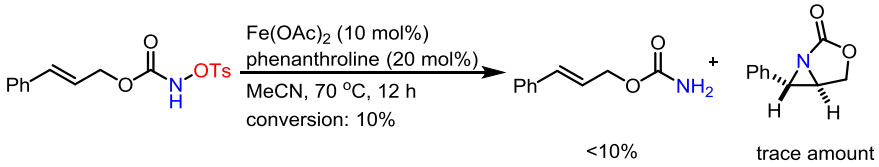
During the optimization process, *O*-alkyl hydroxycarbamates and *O*-sulfonyl hydroxycarbamates were both screened. It was found that *O*-alkyl hydroxycarbamates were nonreactive under $K_4Fe(CN)_6$ (70 ºC), $Fe(NTf_2)_2$ and $Fe(OAc)_2$ conditions. Full recovery of starting material was obtained in each case. *O*-sulfonyl hydroxycarbamates displayed a few undesired reaction patterns listed below.

1) $K_4Fe(CN)_6$ + phenanthroline (70 ºC)

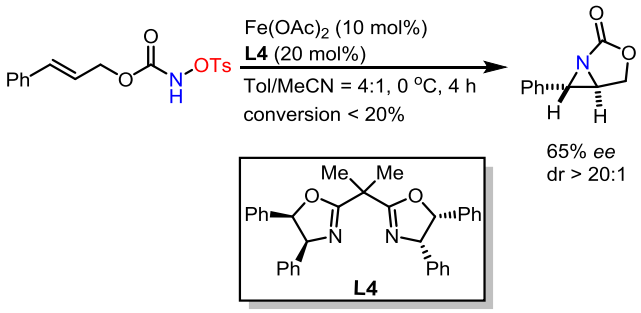


2) $Fe(NTf_2)_2$ + phenanthroline/chiral BOX ligands **L4** (0 ºC): full recovery of the starting material

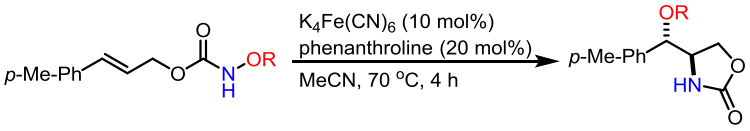
3) $Fe(OAc)_2$ + phenanthroline at RT



4) $Fe(OAc)_2$ + chiral BOX ligands **L4** at 0 ºC:



2.2.4.2 Diastereoselectivity Optimization of para-Methyl Substituted Substrate



R group	dr
R = benzoyl	1:1
R = 2,4-dichlorobenzoyl	1.7:1
R = 4-CO_2Mebenzoyl	1.8:1
R = 3,5-diCF_3benzolyl	2.1:1
R = 4-CNbenzoyl	3.1:1

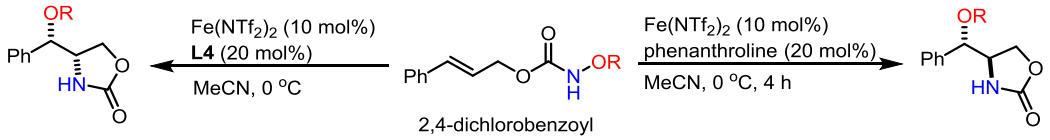
Table 1. T he Diastereoselectivity Optimization of *para*-Methyl Substituted Substrate

For $K_4Fe(CN)_6$-catalyzed reaction, the major diastereomer from the *trans* olefin is the *anti*-addition product, which can be obtained through either intramolecular *suprafacial* ligand (benzoate) transfer after C-C sigma bond rotation or intermolecular *antarafacial* ligand transfer

before C-C sigma bond rotation. From the crossover experiment under the $K_4Fe(CN)_6$-catalyzed conditions, it is possible intermolecular ligand transfer occurs. Therefore, the *antarafacial* ligand transfer before C-C sigma bond rotation might be accountable for a high *dr*. In principle, *para*-methyl-phenyl can further stabilize the radical, and allows for more time of C-C sigma bond rotation before the *antarafacial* ligand transfer, which leads to low *dr*.

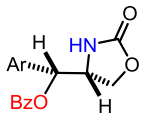
Presumably, more electron-deficient benzoates will be transferred to benzyl radical faster (reminiscent of both Jacobsen and Kochi's ligand electronic tuning to influence the *dr* of epoxidation), so that it can outcompete the *dr* erosion effect from the radical stabilizing groups on substrates.

For $Fe(OAc)_2$ and $Fe(NTf_2)_2$-catalyzed reactions, totally different mechanism might operate. We found the complementary diastereoselectivities were achieved with achiral and chiral ligands.



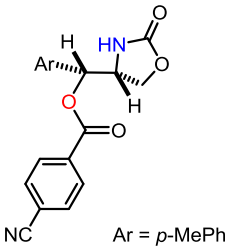
2.2.4.3 General Procedure for Key Reaction Set Up

To a flame-dried schlenk tube were added $K_4Fe(CN)_6$ (0.02 mmol) and phenanthroline (0.04 mmol). After evacuation upon oil pump and refill with Ar three times, anhydrous and degassed MeCN (3 mL) was added. The obtained suspension was stirred vigorously at room temperature for 30 minutes, after which time the substrate (0.2 mmol) was added. The reaction mixture was heated at 70 ºC until all the starting material was fully consumed. The reaction mixture was cooled and concentrated to a residue, which was chromatographed by using 1:1 hexane and ethyl acetate as the eluant to give the designed aminohydroxylation product (40-92% yield).



S4-1

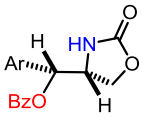
2-Oxooxazolidin-4-yl)(phenyl)methyl benzoate (**S4-1**)[38]: 89% yield from *E* substrate, 75% yield from *Z* substrate, Colorless oil, ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.09 (2H, d, *J* = 7.6 Hz), 7.63 (1H, t, *J* = 7.6 Hz), 7.49 (2H, t, *J* = 7.6 Hz), 7.43-7.39 (5H, m), 6.05 (1H, d, *J* = 6.0 Hz), 5.29 (1H, s), 4.49 (2H, d, *J* = 6.8 Hz), 4.37-4.32 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 165.4, 159.0, 135.5, 133.7, 129.8, 129.2, 129.1, 128.7, 126.6, 75.9, 66.5, 56.2; IR (film) ν_{max}, 3279 (w), 1750 (s), 1745 (s), 1736 (s), 1601 (w), 1451 (m), 1381 (m), 1265 (s), 1178(m), 1108 (s), 1069 (m), 1025 (s), 939 (m), 710 (s) cm^{-1}; HRMS (ESI-TOF) for $C_{17}H_{16}NO_4$ [$M+H^+$] calcd 298.1079, found 298.1065.



S4-2

2-Oxooxazolidin-4-yl)(p-tolyl)methyl 4-cyanobenzoate (**S4-2**): 81% yield, ^{1}H NMR ($CDCl_3$, 400 MHz): major isomer: δ ppm 8.18 (2H, d, *J* = 8.0 Hz), 7.78 (1H, t, *J* = 8.0 Hz), 7.31-7.22 (4H, m), 6.15 (1H, s), 5.91 (1H, d, *J* = 4.8 Hz), 4.40-4.36 (2H, m), 4.21-4.19 (1H, m), 2.36 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 163.9, 159.1, 139.7, 133.1, 132.5, 131.9, 130.3, 130.0, 126.7, 117.8, 78.4, 66.5, 56.2, 21.2; minor isomer: δ ppm 8.18 (2H, d, *J* = 8.0 Hz), 7.78 (1H, t, *J* = 8.0 Hz), 7.31-7.22 (4H, m), 6.03 (1H, d, *J* = 4.8 Hz), 5.72 (1H, s), 4.48-4.46 (1H, m), 4.40-4.36 (1H, m), 2.36 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 163.9, 158.9, 139.5, 133.1, 132.4, 131.7, 130.3, 129.9, 126.6, 117.0, 76.7, 66.3, 56.0, 21.2; IR for the mixture of 2

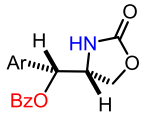
diasteromers (film) ν_{max}, 3318 (w), 1730 (s), 1728 (s), 1635 (w), 1450 (m), 1380 (m), 1271 (s), 1177 (m), 1103 (s), 1018 (m), 910 (m), 737 (s) cm^{-1}; HRMS (ESI-TOF) for $C_{19}H_{15}N_2O_4$ [M-H^+] calcd 335.1032, found 335.1036.



Ar = *p*-CO_2MePh

S4-3

Methyl 4-((benzoyloxy)((2-oxooxazolidin-4-yl)methyl)benzoate (**S4-3**): 75% yield, Colorless oil, ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.08-8.06 (4H, m), 7.65-7.61 (1H, m), 7.51-7.48 (4H, m), 6.10 (1H, d, *J* = 5.2 Hz), 6.00 (1H, s), 4.46-4.42 (2H, m), 4.35-4.30 (1H, m), 3.93 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 166.3, 165.3, 159.1, 140.3, 133.8, 130.9, 130.3, 129.8, 129.0, 128.7, 126.5, 75.5, 66.1, 56.1, 52.3; IR (film) ν_{max}, 3273 (w), 1752 (s), 1747 (s), 1560 (w), 1496 (w), 1267 (s), 1149 (w), 1109 (s), 1019 (w), 900 (w), 713 (s) cm^{-1}; HRMS (ESI-TOF) for $C_{19}H_{18}NO_6$ [M+H^+] calcd 356.1134, found 356.1125.

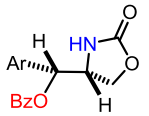


Ar = 3-ClPh

S4-4

3-Chlorophenyl-2-oxooxazolidin-4-yl)methyl benzoate (**S4-4**): 74% yield, Colorless oil, ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.10-8.07 (2H, m), 7.65-7.61 (1H, m), 7.49 (2H, d, *J* = 8.0 Hz), 7.40-7.26 (4H, m), 6.16 (1H, s), 6.02 (1H, d, *J* = 5.2 Hz), 4.49-4.42 (2H, m), 4.32-4.28 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 165.3, 159.2, 137.5, 135.2, 133.8, 130.4, 129.9, 129.3, 129.0, 128.7, 126.7, 124.8, 75.3, 66.3, 56.2; IR (film) ν_{max}, 3274 (w), 1750 (s), 1737 (s),1560 (w), 1477 (m), 1451 (m), 1407 (m), 1262 (s), 1179 (m), 1107 (s), 1069 (m), 1026 (s),

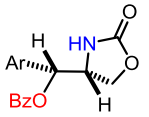
939 (m), 765 (m), 711 (s) cm^{-1}; HRMS (ESI-TOF) for $C_{17}H_{15}NO_4Cl$ $[M+H^+]$ calcd 332.0690, found 332.0690.



Ar = 3-Py

S4-5

(2-Oxooxazolidin-4-yl)(pyridin-4-yl)methyl benzoate (**S4-5**): 80% yield, White solid, mp: 183-185 °C; ^{1}H NMR (MeOD-d_4, 400 MHz): δ ppm 8.71 (1H, s), 8.56 (1H, s), 8.14-8.12 (2H, m), 7.99 (1H, d, J = 8.0 Hz), 7.66 (1H, t, J = 7.6 Hz), 7.55-7.48 (3H, m), 6.12 (1H, d, J = 3.6 Hz), 4.53-4.46 (3H, m); ^{13}C NMR (MeOD-d_4, 100 MHz): δ ppm 165.2, 160.5, 149.1, 147.7, 135.6, 133.5, 132.4, 129.4, 129.1, 128.4, 124.1, 74.4, 65.9, 55.7; IR (film) ν_{max}, 3241 (w), 1721 (s), 1668 (s), 1559 (w), 1461 (m), 1451 (m), 1316 (m), 1261 (s), 1179 (m), 1107 (s), 1069 (s), 1025 (s), 937 (m), 766 (m) cm^{-1}; HRMS (ESI-TOF) for $C_{16}H_{15}N_2O_4$ $[M+H^+]$ calcd 299.1032, found 299.1027.

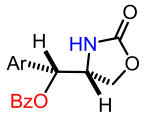


Ar = 1-Naphth

S4-6

Naphthalen-1-yl(2-oxooxazolidin-4-yl)methyl benzoate (**S4-6**): 81% yield, White solid, mp: 115-117 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.17-8.11 (3H, m), 7.93-7.87 (2H, m), 7.68-7.47 (7H, m), 6.91 (1H, d, J = 4.8 Hz), 5.72 (1H, s), 4.64-4.60 (1H, m), 4.55-4.51 (1H, m), 4.39-4.35 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 165.5, 159.1, 133.9, 133.7, 131.3, 130.2, 129.9, 129.7, 129.3, 129.2, 128.7, 127.2, 126.3, 125.3, 124.3, 122.4, 72.9, 66.2, 55.6; IR (film) ν_{max}, 3298 (w), 1738 (s), 1724 (s), 1600 (w), 1402 (m), 1267 (s), 1178 (w), 1109 (m), 1070

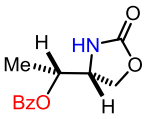
(m), 1027 (m), 765 (m), 712 (s) cm^{-1}; HRMS (ESI-TOF) for $C_{21}H_{18}NO_4$ $[M+H^+]$ calcd 348.1236, found 348.1247.



Ar = Ph-C≡C

S4-7

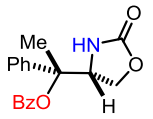
1-(2-Oxooxazolidin-4-yl)-3-phenylprop-2-yn-1-yl benzoate (**S4-7**): 92% yield from *E* substrate, 90% yield from *Z* substrate, Colorless oil, Major isomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.02 (2H, d, J = 8.0 Hz), 7.61-7.59 (1H, m), 7.57-7.44 (4H, m), 7.39-7.26 (3H, m), 6.54 (1H, s), 5.82 (1H, d, J = 4.2 Hz), 4.61-4.56 (1H, m), 4.53-4.50 (1H, m), 4.33-4.31 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 165.2, 159.5, 133.8, 132.2, 130.0, 129.4, 128.9, 128.6, 128.4, 121.1, 87.8, 81.7, 66.5, 66.2, 55.1; minor isomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.99 (2H, d, J = 8.0 Hz), 7.61-7.59 (1H, m), 7.57-7.44 (4H, m), 7.39-7.26 (3H, m), 6.48 (1H, s), 5.90 (1H, d, J = 2.4 Hz), 4.61-4.56 (1H, m), 4.53-4.50 (1H, m), 4.33-4.31 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 165.3, 159.5, 133.3, 131.6, 130.1, 129.4, 128.9, 128.6, 128.3, 121.1, 88.0, 81.4, 66.4, 65.9, 55.2; IR for the two isomers (film) ν_{max}, 3264 (w), 1754 (s), 1721 (s), 1601 (m), 1491 (w), 1406 (m), 1315 (m), 1262 (s), 1178 (w), 1094 (m), 1025 (m), 932 (w), 758 (m), 711 (s), 691 (s) cm^{-1}; HRMS (ESI-TOF) for $C_{19}H_{15}NO_4Na$ $[M+Na^+]$ calcd 344.0899, found 344.0912.



S4-8

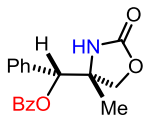
1-(2-Oxooxazolidin-4-yl)ethyl benzoate (**S4-8**): 85% yield, Colorless oil, Major isomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.03 (2H, d, J = 8.0 Hz), 7.58 (1H, t, J = 7.2 Hz), 7.45 (2H, t, J = 7.6 Hz), 6.70 (1H, s), 5.23-5.17 (1H, m), 4.54-4.48 (1H, m), 4.44-4.36 (1H, m), 4.09-4.03

(1H, m), 1.37 (3H, d, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 165.8, 160.0, 133.4, 129.7, 129.6, 128.5, 71.2, 66.3, 55.7, 15.2; minor isomer: ^{1}H NMR (CDCl3, 400 MHz): δ ppm 8.03 (2H, d, J = 8.0 Hz), 7.58 (1H, t, J = 7.2 Hz), 7.45 (2H, t, J = 7.6 Hz), 6.84 (1H, s), 5.17-5.13 (1H, m), 4.54-4.48 (1H, m), 4.28-4.25 (1H, m), 4.09-4.03 (1H, m), 1.37 (3H, d, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 165.8, 160.0, 133.4, 129.7, 129.6, 128.5, 71.5, 66.8, 55.7, 15.7; IR for the two isomers (film) ν_{max}, 3298 (w), 1755 (s), 1736 (s), 1722 (s), 1541 (w), 1276 (s), 1150 (w), 1110 (m), 960 (w), 729 (w), 712 (s) cm^{-1}; HRMS (ESI-TOF) for $C_{12}H_{14}NO_4$ [M+H$^+$] calcd 236.0923, found 236.0925.



S4-9

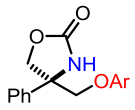
1-(2-Oxooxazolidin-4-yl)-1-phenylethyl benzoate (**S4-9**): 81% yield, Colorless oil, Major isomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.07 (2H, d, J = 8.0 Hz), 7.61 (1H, t, J = 7.2 Hz), 7.49 (2H, t, J = 7.2 Hz), 7.42-7.33 (5H, m), 6.32 (1H, s), 4.33-4.31 (2H, m), 4.23-4.20 (1H, m), 2.07 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 164.6, 159.6, 139.5, 133.4, 129.7, 129.0, 128.6, 128.4, 125.1, 83.8, 65.7, 61.8, 18.7; IR (film) ν_{max}, 3298 (w), 1755 (s), 1722 (s), 1540 (w), 1276 (s), 1150 (w), 1110 (m), 957 (w), 735 (w), 712 (s) cm^{-1}; HRMS (ESI-TOF) for $C_{18}H_{18}NO_4$ [M+H$^+$] calcd 312.1236, found 312.1243.



S4-10

(4-Methyl-2-oxooxazolidin-4-yl)(phenyl)methyl benzoate (**S4-10**): 71% yield, Colorless oil, Major isomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.10-7.37 (10H, m), 5.99 (1H, s), 5.90 (1H, s), 4.54 (1H, d, J = 8.8 Hz), 4.14 (1H, d, J = 8.8 Hz), 1.39 (3H, s); ^{13}C NMR

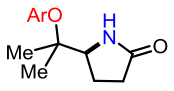
($CDCl_3$, 100 MHz): δ ppm 165.4, 158.9, 135.2, 133.6, 129.9, 129.3, 128.8, 128.7, 127.2, 79.3, 73.5, 23.3; minor isomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.10-7.37 (10H, m), 6.22 (1H, s), 5.99 (1H, s), 4.56 (1H, m), 4.10 (1H, d, J = 8.8 Hz), 1.48 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 165.4, 158.9, 135.2, 133.3, 129.9, 129.8, 128.8, 128.7, 127.3, 79.0, 72.8, 23.0; IR for the two isomers (film) ν_{max}, 3280 (w), 1752 (s), 1721 (s), 1534 (w), 1276 (s), 1130 (w), 1111 (m), 970 (w), 735 (w), 716 (s) cm^{-1}; HRMS (ESI-TOF) for $C_{18}H_{18}NO_4$ [M+H$^+$] calcd 312.1236, found 312.1243.



Ar = *p*-CO_2Me-benzoyl

S4-11

Methyl ((2-oxo-4-phenyloxazolidin-4-yl)methyl) terephthalate (**S4-11**): 72% yield, White solid, mp: 207-209 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.11-8.05 (4H, m), 7.48-7.36 (5H, m), 6.48 (1H, s), 4.77 (1H, d, J = 8.8 Hz), 4.70-4.63 (2H, m), 4.78 (1H, d, J = 8.4 Hz), 3.96 (3H, s); ^{13}C NMR (DMSO-d_6, 100 MHz): δ ppm 165.9, 165.0, 158.7, 140.9, 134.3, 133.5, 130.1, 129.9, 129.2, 128.5, 125.8, 72.8, 70.2, 63.1, 53.0; IR (film) ν_{max}, 3279 (w), 1750 (s), 1718 (s), 1435 (m), 1399 (w), 1267 (s), 1106 (m), 1018 (m), 750 (s), 727 (s) cm^{-1}; HRMS (ESI-TOF) for $C_{19}H_{18}NO_6$ [M+H$^+$] calcd 356.1134, found 356.1123.

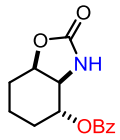


Ar = *p*-CO_2Me-benzoyl

S4-12

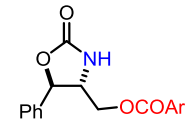
Methyl (2-(5-oxopyrrolidin-2-yl)propan-2-yl) terephthalate (**S4-12**): 76% yield, White solid, mp: 160-162 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.10 (d, 2H, J = 8.4 Hz), 8.01 (2H, d, J = 8.0 Hz), 6.62 (1H, s), 4.08 (1H, t, J = 6.8 Hz), 3.97 (1H, s), 2.43-2.26 (3H, m), 2.04-

2.01 (1H, m), 1.66 (3H, s), 1.62 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 178.3, 166.2, 164.7, 134.9, 134.0, 129.6, 129.4, 84.8, 61.8, 52.5, 30.0, 22.4, 22.1, 20.4; IR (film) ν_{max}, 2917 (w), 1695 (s), 1596 (m), 1499 (w), 1457 (w), 1389 (w), 1277(s), 1118 (m), 731 (m), cm^{-1}; HRMS (ESI-TOF) for $C_{16}H_{20}NO_5$ [M+H$^+$] calcd 306.1341, found 306.1348.



S4-13

2-Oxooctahydrobenzo[d]oxazol-4-yl benzoate (S4-13): 75% yield, White solid, mp: 158-160 $^{\circ}$C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.03 (d, 2H, J = 8.0 Hz), 7.60 (1H, t, J = 7.2 Hz), 7.47 (2H, t, J = 7.6 Hz), 6.04 (1H, s), 5.02-4.97 (1H, m), 4.84-4.83 (1H, m), 3.76-3.73 (1H, m), 2.24-2.13 (2H, m), 1.80-1.73 (3H, m), 1.58-1.49 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 166.2, 159.5, 133.5, 129.7, 129.6, 128.5,76.5, 76.3, 56.8, 26.6, 26.2, 17.0; IR (film) ν_{max}, 2926 (w), 1752 (m), 1275 (w), 1261(s), 1151 (m), 750 (m), cm^{-1}; HRMS (ESI-TOF) for $C_{14}H_{16}NO_4$ [M+H$^+$] calcd 262.1079, found 262.1085.



Ar = *p*-CO_2MePh

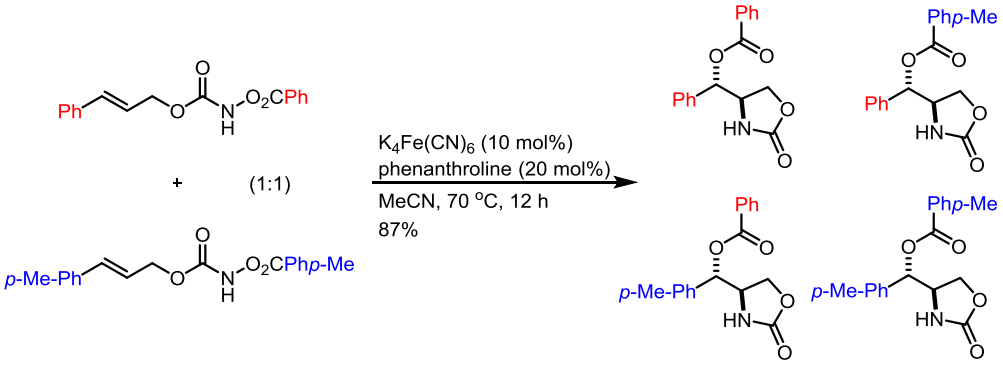
S4-14

methyl ((2-oxo-5-phenyloxazolidin-4-yl)methyl) terephthalate (S4-14): 40% yield, White solid, mp: 183-185 $^{\circ}$C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.15-8.08 (m, 4H), 7.43 (5H, s), 5.77 (1H, s), 5.11 (1H, d, J = 5.6 Hz), 4.65-4.61 (1H, m), 4.49-4.45 (1H, m), 4.16-4.15 (1H, m), 3.98 (3H, s); ^{13}C NMR (d^6-DMSO, 100 MHz): δ ppm 166.0, 165.2, 158.5, 139.7, 134.2, 133.7, 130.2, 129.9, 129.3, 129.2, 126.4, 78.8, 66.4, 58.6, 53.0; IR (film) ν_{max}, 3377 (w), 1757

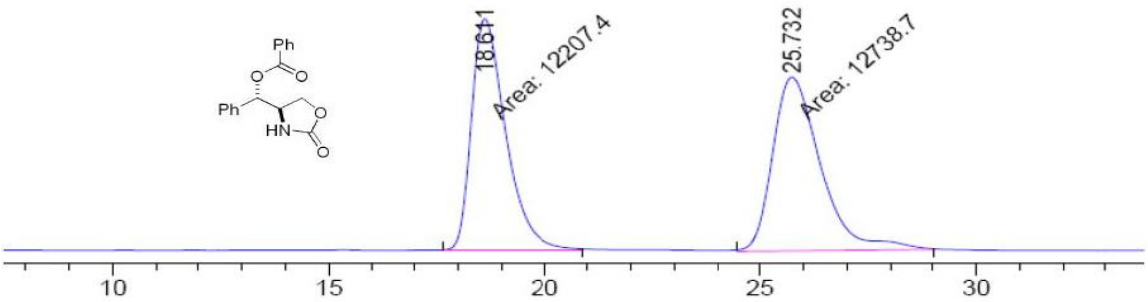
(m), 1721 (m), 1403 (m), 1275 (s), 1119 (s), 1019 (m), 730 (m), cm^{-1}; HRMS (ESI-TOF) for $C_{19}H_{18}NO_6$ [M+H$^+$] calcd 356.1134, found 356.1128.

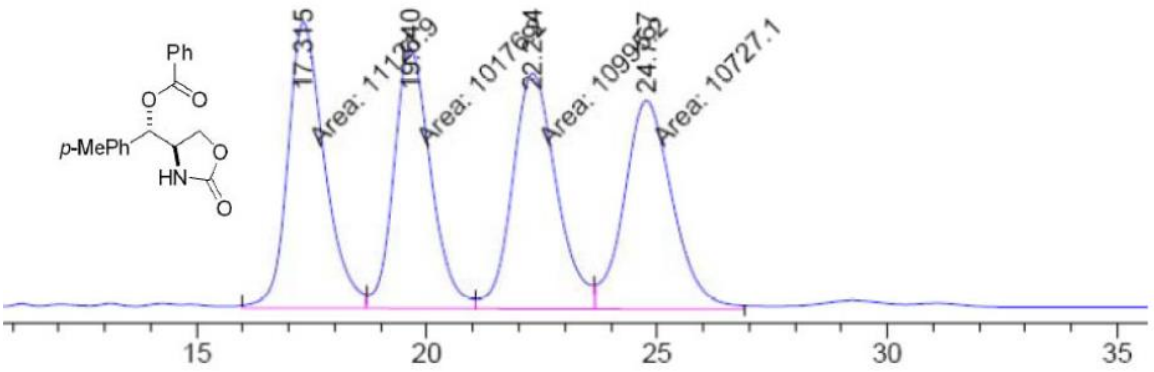
2.2.5 $K_4Fe(CN)_6$-Catalyzed Crossover Experiment

To a flame-dried Schleck tube was added $K_4Fe(CN)_6$ (0.02 mmol) and phenanthroline (0.04 mmol). After evacuation upon oil pump and refill with Ar three times, anhydrous and degassed MeCN (3 mL) was added. The obtained suspension was stirred vigorously at room temperature for 30 minutes, after which time the two substrates with the same equivalence (0.1 mmol for each) were added. The reaction mixture was heated at 70 ºC until all the starting material was fully consumed. The reaction mixture was cooled and concentrated to a residue, which was filtered through a very short column. The obtained solution was then concentrated upon rotavap and analyzed on chiral HPLC (Chiralcel OD-H, 1.0 mL/min, 210 nm, 20% *i*-PrOH in hexane).



HPLC traces for four possible cyclization products:

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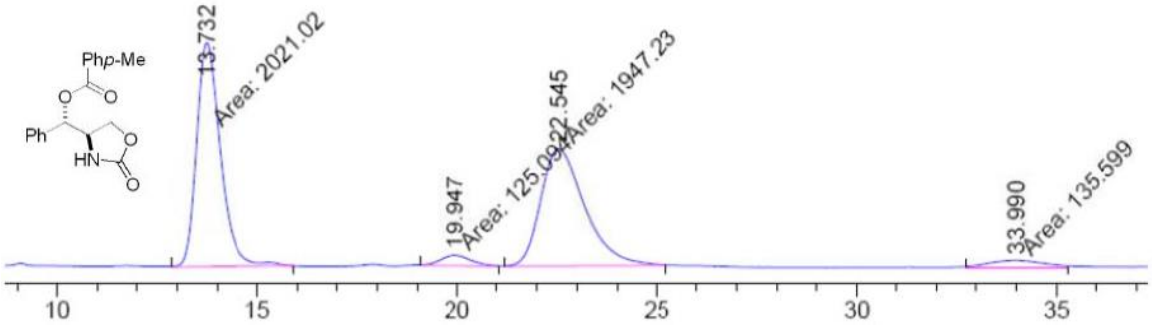
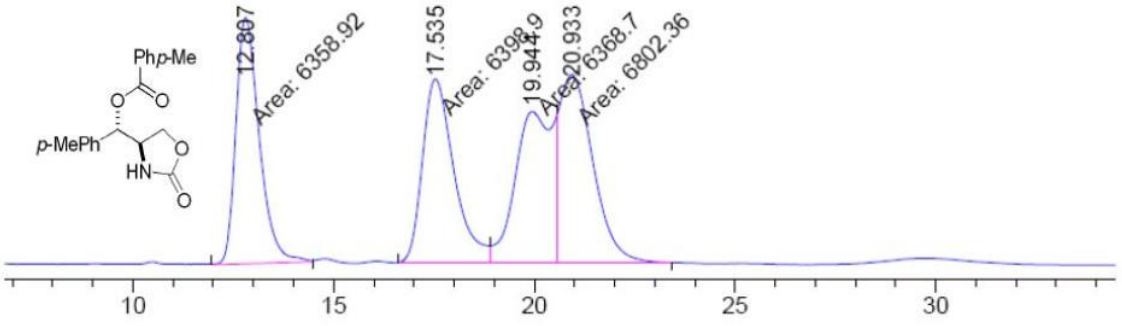
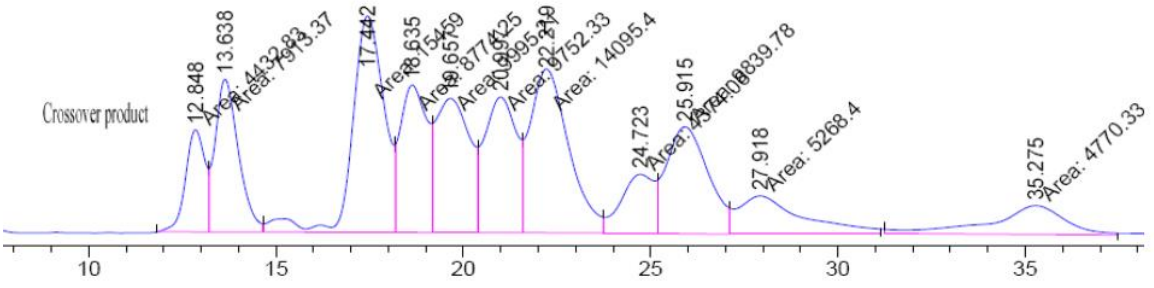
HN
17.315
Area: 1112
Area: 1017
Area: 1099
24.792
Area: 10727.1
15
20
25
30
35


Php-Me
Ph
HN
13.732
Area: 2021.02
19.947
Area: 125.094
22.545
Area: 1947.23
33.990
Area: 135.599
10
15
20
25
30
35


Php-Me
p-MePh
HN
12.807
Area: 6358.92
17.535
Area: 6398
19.944.9
Area: 6368.7
20.933
Area: 6802.36
10
15
20
25
30


Crossover product
12.848
13.638
Area: 7933.37
17.442
Area: 14095.4
24.723
25.915
27.918
Area: 5268.4
35.275
Area: 4770.33
10
15
20
25
30
35

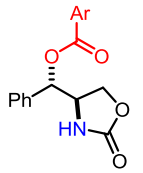
2.2.6 Iron(II)-Catalyzed Enantioselective Olefin Aminohydroxylation

2.2.6.1 Procedure for Fe(II)-Catalyzed Racemic Aminohydroxylation Reaction

To a flame-dried Schleck tube was added $K_4Fe(CN)_6$ (0.02 mmol) and phenanthroline (0.04 mmol) respectively. After evacuation upon oil pump and refill with Ar three times, anhydrous and degassed MeCN (3 mL) was added. The obtained suspension was stirred vigorously at room temperature for 30 minutes, after which time the substrate **9a** or **9b** (0.2 mmol) was added. The reaction mixture was heated at 70 ºC until all the starting material was fully consumed. The reaction mixture was cooled and concentrated to a residue, which was chromatographed by using 1:1 hexane and ethyl acetate as the eluant to give the designed racemic aminohydroxylation product (85% yield, *dr* = 3.6:1).

2.2.6.2 Procedure for Fe(II)-Catalyzed Asymmetric Aminohydroxylation Reaction

To a flame-dried schlenk tube were added $Fe(NTf_2)_2$ (0.01 mmol) and chiral ligand **L3** (0.02 mmol) respectively. After evacuation upon oil pump and refill with Ar gas three times, anhydrous and degassed acetonitrile (2 mL) was added. The obtained mixture was stirred vigorously at room temperature for 60 minutes. Substrate **9a** or **9b** (0.1 mmol) in 1 mL of anhydrous and degassed MeCN was then added. The reaction mixture was stirred at -10 ºC for 12 hours. The reaction mixture was then quenched by Sat. $NaHCO_3$, and then extracted with ethyl acetate. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated in *vacuo* to afford the crude product, which was purified by flash column chromatography using 50 % ethyl acetate-hexane (68% yield, *dr* > 20:1, 82% *ee*).



Ar =2,4-Cl_2-Ph

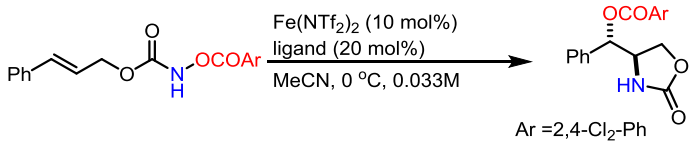
11

2-Oxooxazolidin-4-yl)(phenyl)methyl 2,4-dichlorobenzoate (**11**): ^{1}H NMR ($CDCl_3$, 400 MHz): $[\alpha]_D^{20}$ = -8.8 (*c* = 1.3, CH_2Cl_2); *syn*-isomer: δ ppm 7.90 (2H, d, *J* = 8.4 Hz), 7.51 (1H, s), 7.43 (5H, s), 7.35 (1H, d, *J* = 8.4 Hz), 6.04 (1H, s), 5.93 (1H, d, *J* = 5.6 Hz), 4.35-4.31 (2H, m), 4.21-4.20 (1H, m); *anti*-isomer: δ ppm 7.90 (2H, d, *J* = 8.4 Hz), 7.51 (1H, s), 7.43 (5H, s), 7.35 (1H, d, *J* = 8.4 Hz), 6.04 (1H, d, *J* = 6.0 Hz), 5.14 (1H, s), 4.52-4.45 (2H, m), 4.38-4.33 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): *syn*-isomer: δ ppm 163.6, 158.9, 139.2, 135.0, 134.9, 133.1, 131.2, 129.5, 129.3, 127.4, 127.2, 127.0, 78.6, 66.2, 56.1; *anti*-isomer: δ ppm 163.6, 158.9, 139.3, 135.0, 134.9, 133.2, 131.2, 129.5, 129.4, 127.4, 127.3, 127.1, 78.8, 66.2, 56.2; IR (film) ν_{max}, 3285 (w), 1738 (m), 1653 (m), 1584 (m), 1455 (m), 1376 (m), 1276 (w), 1231(s), 1145 (m), 1100 (m), 1045 (m), 733 (m), 696 (s) cm^{-1}; HRMS (ESI-TOF) for $C_{17}H_{12}Cl_2NO_4$ [M-H^+] calcd 364.0143, found 364.0142.

2.2.6.3 Reaction Optimization of Asymmetric Aminohydroxylation Reaction

Parameters below were further optimized upon following the procedure of Fe(II)-catalyzed asymmetric aminohydroxylation reaction.

1) Ligand screen



Ar =2,4-Cl_2-Ph

Ligand	ee (%)
L1	37
L2	45
L3	65
L4	82
L5	82

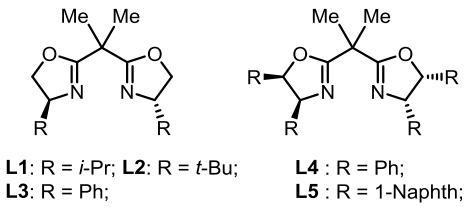
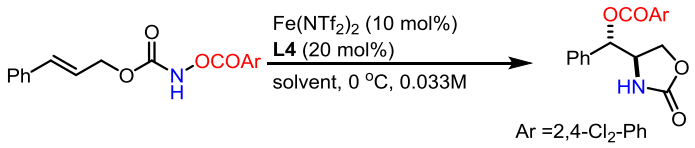


Table 2. Ligand Screening for Reaction Optimization

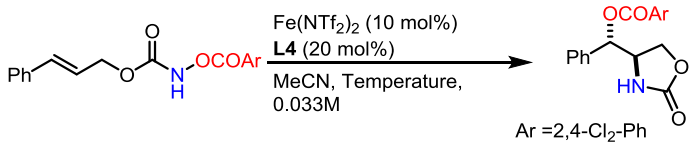
2) Solvent screen



Solvent	ee (%)
Toluene	59
Toluene/MeCN = 40/1	63
Toluene/MeCN = 20/1	71
Toluene/MeCN = 10/1	73
Toluene/MeCN = 4/1	77
MeCN	82

Table 3. Solvent Screening for Reaction Optimization

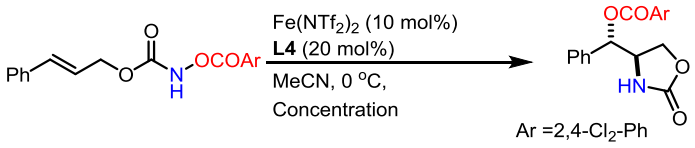
3) Temperature screen



Temperature	ee (%)
Room temperature	65
0 °C	82
-10 °C	82
-20 °C	83

Table 4. Temperature Screening for Reaction Optimization

4) Concentration screen



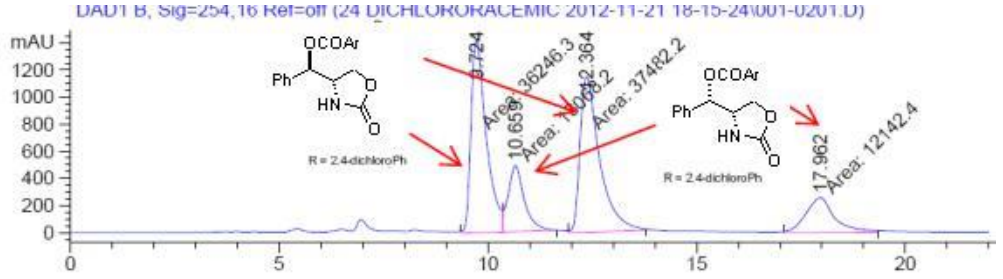
Concentration	ee (%)
0.1 M	75
0.05 M	79
0.03 M	82
0.01 M	79

Table 5. Concentration Screening for Reaction Optimization

2.2.6.4 HPLC Data

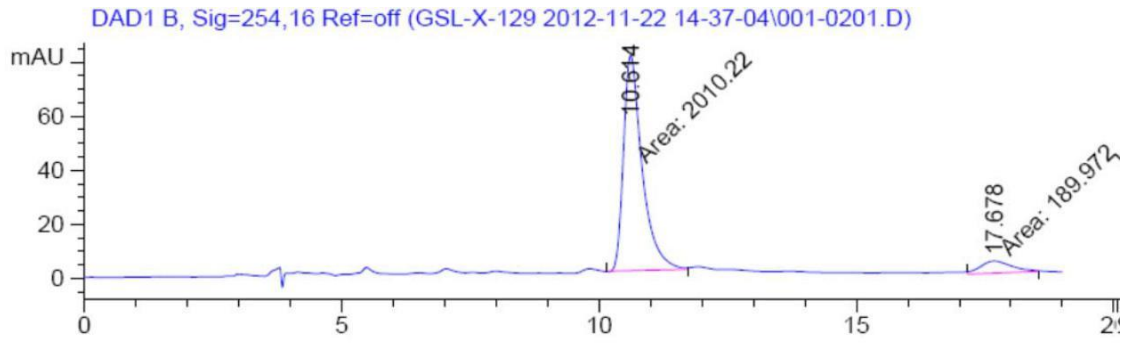
The samples were analyzed by Chiral HPLC analysis (Chiralcel AD-H, 1.0 mL/min, 254 nm, 20% *i*-PrOH in hexane).

Racemic sample:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.724	MF	0.4256	3.62463e4	1419.45117	36.6350
2	10.659	FM	0.4470	1.30682e4	487.22986	13.2083
3	12.364	MM	0.5442	3.74822e4	1147.95288	37.8841
4	17.962	MM	0.7901	1.21424e4	256.12671	12.2726

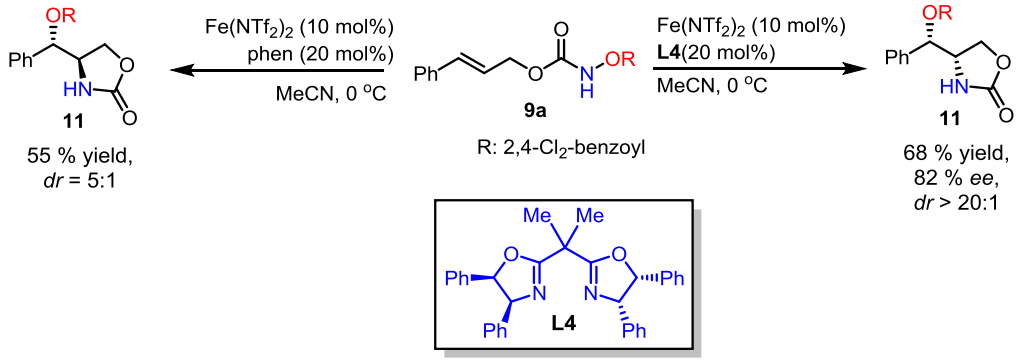
Fe^{II}-catalyzed tethered asymmetric aminohydroxylation reaction:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.614	MM	0.4207	2010.21692	79.63549	91.3657
2	17.678	MM	0.7056	189.97186	4.48701	8.6343

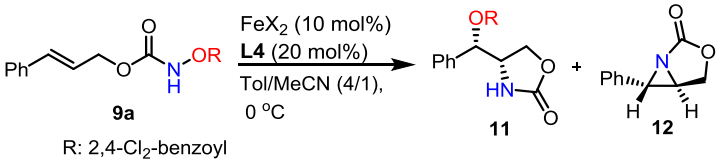
2.2.6.5 Ligand Effect over Diastereoselectivity

An *anti*-amino alcohol was obtained when achiral ligands (including phenanthroline and the tridentate **L4**) was used as a ligand, disregard of iron sources while a *syn*-amino alcohol was obtained when chiral BOX ligands were applied.



2.2.7 Iron(II)-Catalyzed Enantioselective Olefin Aziridination

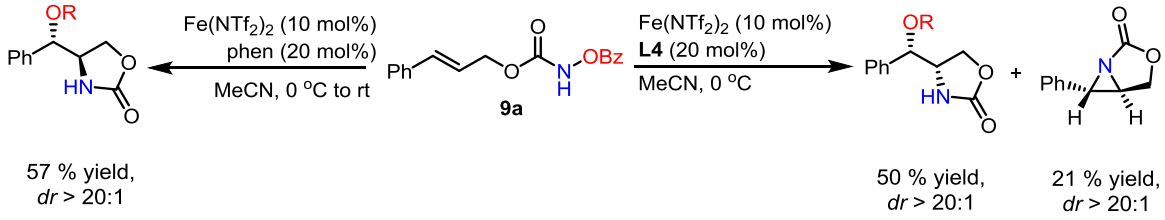
2.2.7.1 Counter ion Effect



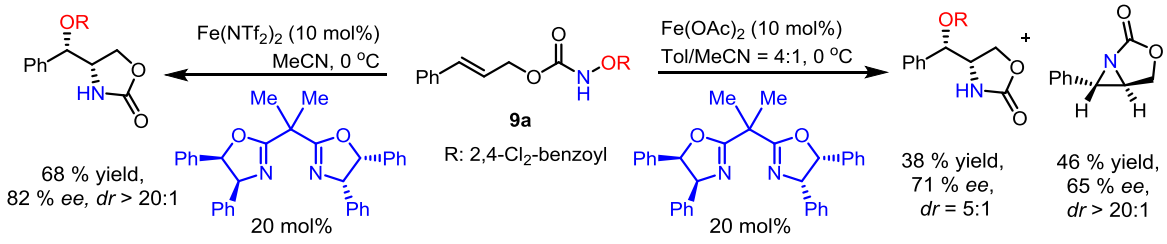
Iron salt	11/12 (crude ^{1}H NMR)	ee of 12 (%)
$Fe(OAc)_2$	1/1.2	65
$Fe(TFA)_2$	1/0.7	61
$Fe(NTf_2)_2$	1/0	n.d.

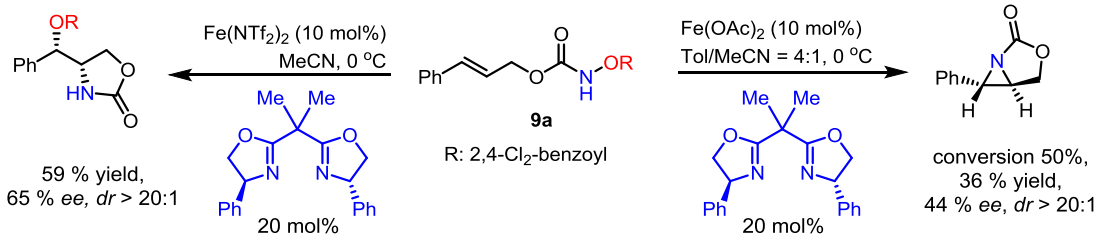
Table 6. Counter Ion Screening for Reaction Optimization

1) Phenanthroline as a ligand



2) Chiral BOX as a ligand





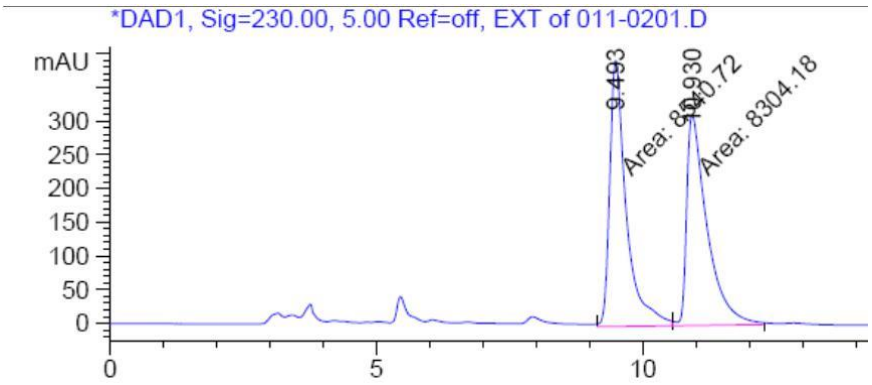
2.2.7.2 Fe(II)-Catalyzed Enantioselective Olefin Aziridination

To a flame-dried Schleck tube was added $Fe(OAc)_2$ (0.01 mmol) and chiral ligand **L4** (0.02 mmol) respectively. After evacuation upon oil pump and refill with Ar gas three times, anhydrous and degassed toluene/acetonitrile (2 mL, v/v = 4/1) was added. The obtained mixture was stirred vigorously at room temperature for 60 minutes. Substrate **9a** or **9b** (0.1 mmol) in 1 mL of anhydrous and degassed toluene/acetonitrile (2 mL, v/v = 4/1) was then added. The reaction mixture was stirred at 0 ºC for 12 hours. The reaction mixture was then quenched by Sat. $NaHCO_3$, and then extracted with ethyl acetate. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated in *vacuo* to afford the crude product, which was purified by flash column chromatography using 50% ethyl acetate-hexane (38% yield of aminohydroxylation product **11** and 46% yield of aziridination product **12**). **12**:[37d] $[\alpha]_D^{20}$ = -1.6 (*c* = 0.2, CH2Cl2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.39-7.37 (3H, m), 7.21 (2H, d, *J* = 8.0 Hz), 4.65 (1H, d, *J* = 9.2 Hz), 4.55 (1H, dd, *J* = 9.2, 5.2 Hz), 3.38 (1H, d, *J* = 3.2 Hz), 3.26-3.25 (1H, m)].

2.2.7.3 HPLC Data

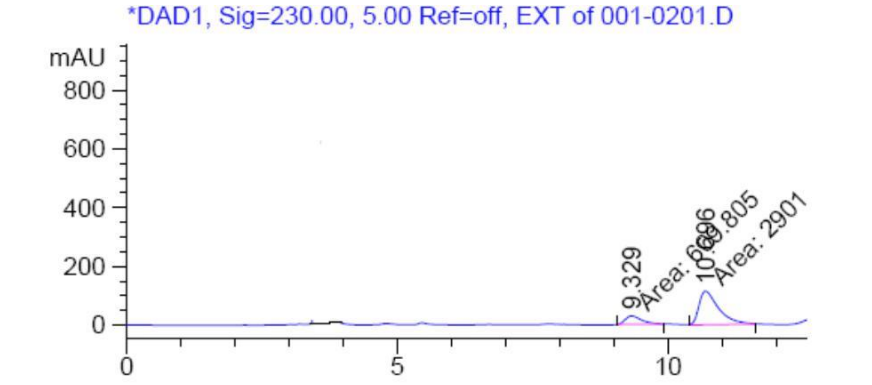
The samples were analyzed by Chiral HPLC analysis (Chiralcel AD-H, 1.0 mL/min, 230 nm, 20% *i*-PrOH in hexane).

Racemic sample (Racemic sample, used as a standard for chiral HPLC analysis, was synthesized by the identical method except for using 20 mol % phenanthroline instead of chiral ligand **L4**):



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.493	MF	0.3615	8540.71582	393.72308	50.7021
2	10.930	FM	0.4438	8304.18066	311.86386	49.2979

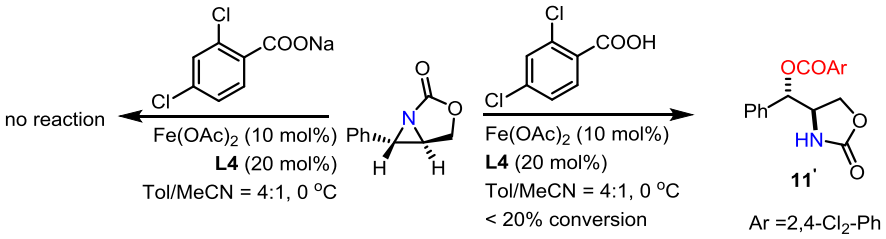
Fe(II)-catalyzed asymmetric aziridination reaction:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.329	MM	0.3521	609.80457	28.86740	17.3671
2	10.696	MM	0.4222	2901.45776	114.53984	82.6329

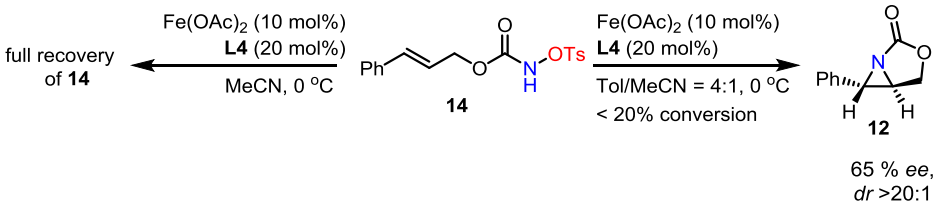
2.2.7.4 Control Experiments

To verify whether or not **11** was obtained through the intermediacy of aziridine **12** in $Fe(OAc)_2$-catalzyed reactions, **12** was subjected to the catalytic reaction conditions. The isomeric aminohydroxylation product **11'** was isolated.



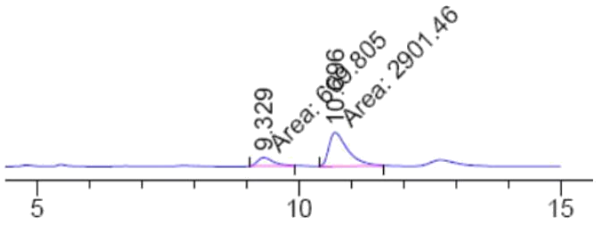
To a flame-dried Schleck tube was added $Fe(OAc)_2$ (0.01 mmol) and chiral ligand **L4** (0.02 mmol) respectively. After evacuation upon oil pump and refill with Ar gas three times, anhydrous and degassed toluene/acetonitrile (2 mL, v/v = 4/1) was added. The obtained mixture was stirred vigorously at room temperature for 60 minutes. Aziridine **12** (0.1 mmol) and 2,4-dichlorobenzoic acid or its sodium salt (0.1 mmol) in 1 mL of anhydrous and degassed toluene/acetonitrile (1 mL, v/v = 4/1) was then added. The reaction mixture was stirred at 0 ºC for 12 hours. The reaction mixture with 2,4-dichlorobenzoic acid was then quenched by Sat. $NaHCO_3$, and then extracted with ethyl acetate. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated in *vacuo* to afford the crude product, which was purified by flash column chromatography using 50 % ethyl acetate-hexane: 15% isolated yield of *anti*-isomer.

2.2.7.5 Olefin Aziridination of Tosyl Hydroxyl Carbamate



To a flame-dried Schleck tube was added $Fe(OAc)_2$ (0.01 mmol) and chiral ligand **10** (0.02 mmol) respectively. After evacuation upon oil pump and refill with Ar gas three times, anhydrous and degassed toluene/acetonitrile (2 mL, v/v = 4/1) was added. The obtained mixture was stirred vigorously at room temperature for 60 minutes. Substrate **14** (0.1 mmol) in 1 mL of

anhydrous and degassed toluene/acetonitrile (2 mL, v/v = 4/1) was then added. The reaction mixture was stirred at 0 ºC for 12 hours. The reaction mixture was then quenched by Sat. $NaHCO_3$, and then extracted with ethyl acetate. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated in *vacuo* to afford the crude product, which was purified by flash column chromatography using 50% ethyl acetate-hexane. From HPLC trace, the *ee* of aziridination product **12** was also 65% (Chiralcel AD-H, 1.0 mL/min, 230 nm, 20% *i*-PrOH in hexane).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.329	MM	0.3521	609.80457	28.86740	17.3671
2	10.696	MM	0.4222	2901.45776	114.53984	82.6329

2.2.8 Procedure of Product Derivatization

82% *ee* 82% *ee*

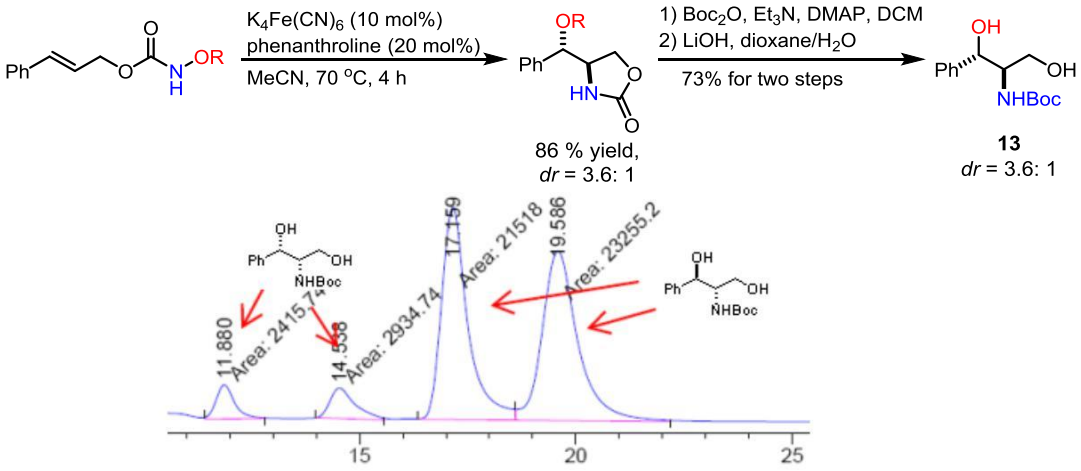
Procedures: [40] A mixture of **11** (37 mg, 0.1 mmol), Boc_2O (32 mg, 0.14 mmol), Et_3N (21 µL, 0.15 mmol) and a catalytic amount of DMAP (10% mol) in CH_2Cl_2 (2 mL) was stirred 1 hour at room temperature. The reaction was quenched by concentrated in a vacuum. Quick

purification of the residue by a short flash chromatography (hexane/ethyl acetate) afforded Boc-protected product in quantitative yield. The above obtained Boc-protected product was dissolved in 1,4-dioxane (2 mL). An aqueous solution of LiOH 2N (0.3 mL, 0.6 mmol) was then added. The mixture was stirred at room temperature for 4 h. The solvent was removed. The resulting crude was purified by flash chromatography (hexane/ethyl acetate) to give 18.7 mg of compound **13**[41] (70 %) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.41-7.30 (5H, m), 5.17 (1H, brs), 5.01 (1H, s), 3.85-3.79 (3H, m), 3.03 (1H, brs), 2.26 (1H, brs), 1.38 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 141.1, 128.5, 127.9, 126.1, 79.9, 74.8, 64.2, 57.2, 28.3. HRMS (ESI-TOF) for $C_{14}H_{22}NO_4$ [M+H$^+$] calcd 269.1472, found 269.1469.

HPLC data of 13:

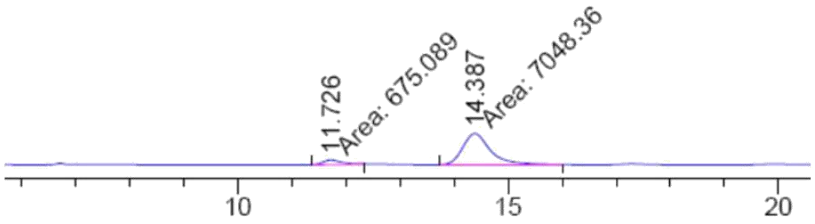
The samples were analyzed by Chiral HPLC analysis (Chiralcel AD-H, 1.0 mL/min, 220 nm, 5% *i*-PrOH in hexane).

Racemic Sample (The racemic sample was gotten through the following route):



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.880	MM	0.4946	2415.74487	81.39605	4.8196
2	14.538	MM	0.6736	2934.74365	72.61868	5.8550
3	17.159	MF	0.7069	2.15180e4	507.32492	42.9298
4	19.586	FM	0.9566	2.32552e4	405.16666	46.3956

Enantio-enriched Sample:

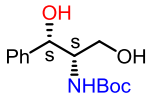


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.726	MM	0.3959	675.08936	28.42159	8.7408
2	14.387	MM	0.5985	7048.35645	196.27458	91.2592

2.2.9 Determination

2.2.9.1 Comparison of Optical Rotation

Comparison of optical rotation of **13** with literature value:[42]

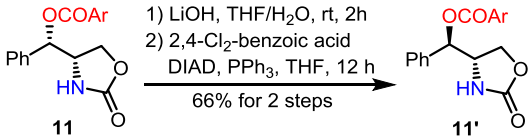


literature value: $[\alpha]_D^{20}$ = +51.5 (c = 1.02, CH_2Cl_2)

experiment value: $[\alpha]_D^{20}$ = +31.7 (c = 0.26, CH_2Cl_2) (82% *ee* from chiral HPLC)

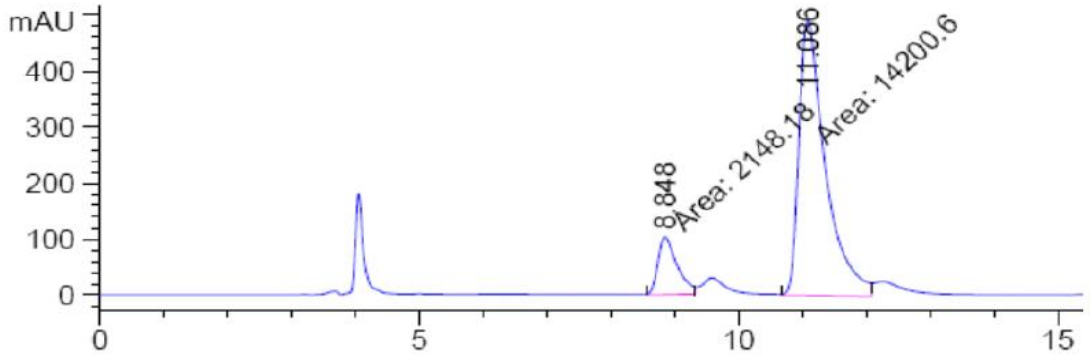
2.2.9.2 Stereospecific Epimerization

To confirm the absolute stereochemistry of the aziridine, the hydrolysis product of **11** was subjected to the Mitsunobu reaction condition.

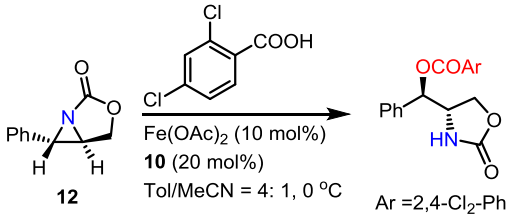


Ar =2,4-Cl_2-Ph

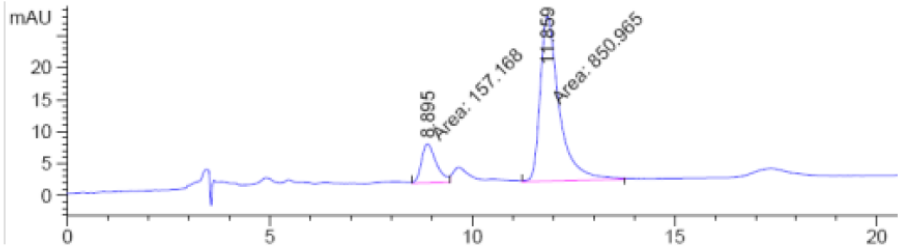
HPLC trace of 11':



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.848	MM	0.3481	2148.18237	102.85355	8.2799
2	11.086	MM	0.4807	1.42006e4	492.31439	91.7201



HPLC trace:

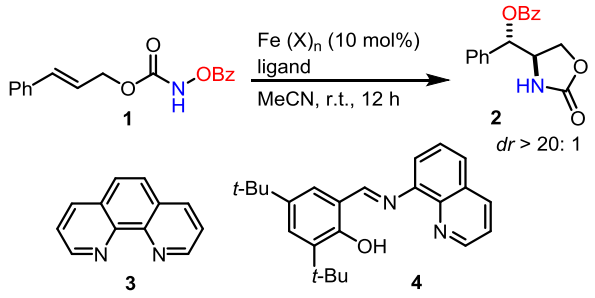


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.895	MF	0.4284	157.16843	6.11477	15.5900
2	11.859	MM	0.5480	850.96515	25.88031	84.4100

2.3 RESULTS

2.3.1 Catalyst Discovery for the Aminohydroxylation

We initiated the catalyst discovery with a cinnamyl alcohol derived substrate **1** that incorporates both a *trans*-disubstituted olefin and a functionalized hydroxylamine. A preliminary inspection revealed that Fe^{II} salts alone are unable to catalyze the reaction at room temperature; however, the reactions are greatly accelerated by a variety of nitrogen-based bidentate and tridentate ligands (Table **7**): ligands **3** and **4** (with π-acceptor character) facilitate more efficient reactions than TMEDA and sparteine (entries 1−4). While Fe^{II}/**3** complexes are able to catalyze the aminohydroxylation, Fe^{III}/**3** complexes are inactive (entry 5). In addition, we observed a significant counterion effect: cyanide (entries 9 and 10) with strong π-acceptor character proves to be superior to bromide (entries 3 and 4), triflate (entry 6), carboxylate (entry 7), and triflimide (entry 8). Re-examination of Fe^{II} cyanide/ligand combinations revealed that $K_4Fe(CN)_6$/**3** can catalyze a highly diastereoselective aminohydroxylation,[16c, 38] delivering an anti-amino alcohol with a stereochemistry complementary to the one obtained through Os-based methods. We discovered that acyl hydroxyl carbamates prove uniquely effective for the desired reaction: both alkyl and sulfonyl hydroxyl carbamates are not viable substrates.



entry[a]	$Fe(X)_n$	ligand (mol%)	conversion[b]	yield[c]
1	$FeBr_2$	none	<10%	<5%
2	$FeBr_2$	sparteine/TMEDA	<40%	<5%
3	$FeBr_2$	**3** (20)	100%	8%

4[d]	$FeBr_2$	**4** (10)	100%	56%
5[e]	$FeBr_3$	**3** (20)	<10%	NA
6	$Fe(OTf)_2$	**3** (20)	50%	5%
7[f]	$Fe(OAc)_2$	**3** (20)	76%	50%
8	$Fe(NTf_2)_2$	**3** (20)	90%	57%
9[d,g,h]	$K_4Fe(CN)_6$	**4** (10)	100%	78%
10[g,h]	$K_4Fe(CN)_6$	**3** (20)	100%	89%

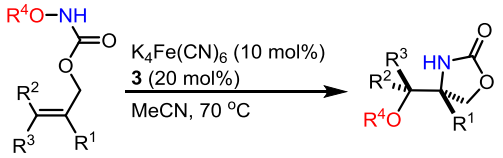
[a]Reactions were carried out under argon at 23 °C unless stated otherwise. [b]Conversions were determined by **^{1}H NMR** analysis with 1,3,5-trimethoxybenzene as an internal standard. [c]Isolated yield. [d]Catalyst was prepared in situ by stirring $FeBr_2$ or $K_4Fe(CN)_6$ with freshly prepared potassium salt of the ligand **4**. [e]The reaction was performed at 45 °C. [f]An aziridine was isolated. [g]The reaction was performed at 70 °C for 4 h. [h]Conversion was less than 5% without ligands. TMEDA = tetramethylethylenediamine, OTf = trifluoromethanesulfonate, NTf_2 = trifluoromethanesulfonimide.

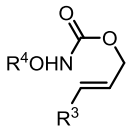
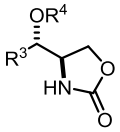
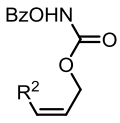
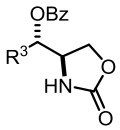
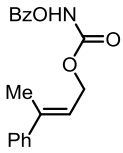
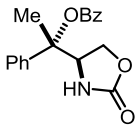
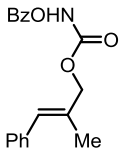
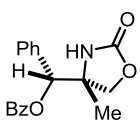
Table 7. Catalyst Discovery for the Aminohydroxylation

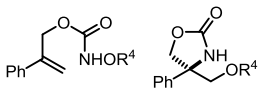
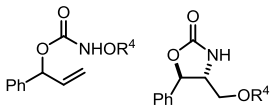
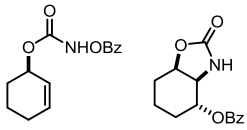
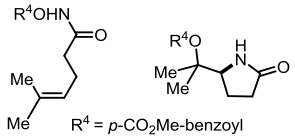
2.3.2 Substrate Scope of Iron-Catalyzed Aminohydroxylation

To explore the scope and limitation of this reaction, we have applied the method to a variety of olefins (Table **8**). *trans*- Disubstituted styrenyl olefins are excellent substrates (*dr* > 20:1) (entries 1−4). Unlike Os-based methods that are not tolerant to basic nitrogen functional groups,[43] the olefin containing a pyridine ring is a viable substrate (entry 4). A *para*-methyl-styrenyl substrate suffers from a total loss of *dr* (entry 5); however, electronic tuning on the benzoyl group increased the *dr* to 3.1:1 (entry 6).[44] *trans*-Disubstituted olefins with 1-naphthyl, alkyl, and alkynyl substituents can participate in the reaction with acceptable yields but diminished diastereoselectivity (entries 7−9, *dr* varies from 2.5:1 to 5:1). We note that the *cis*-disubstituted olefins also afford anti-amino alcohols in this reaction (entries 10−11). The stereochemical convergence (entries 1 and 10) and a related crossover experiment suggest the stepwise nature of the aminohydroxylation. In addition, trisubstituted olefins (entries 12− 13) are suitable substrates (*dr* varies from 2.2:1 to > 20:1). Disubstituted terminal olefins are decent substrates (entry 14), while monosubstituted olefins (entry 15) suffer from lower yields. We also

discovered a cyclohexanol-derived substrate (entry 16) readily participates in the reaction to afford an *anti*-hydroxyl oxazolidinone that was difficult to access with Os-based strategies. Further investigation reveals that nonallylic alcohol based substrates, including an olefin containing hydroxamate, can also undergo smooth reactions (entry 17).



entry	olefin	product	*T* (h)	yield[a]	*dr*[b]
					
1	R^3 = Ph, R^4 = Bz		4	89%	> 20 : 1
2	R^3 = 4-CO_2MePh, R^4 = Bz		10	75%	> 20 : 1
3	R^3 = 3-ClPh, R^4 = Bz		8	74%	> 20 : 1
4	R^3 = 3-Py, R^4 = Bz		12	80%	> 20 : 1
5	R^3 = 4-MePh, R^4 = Bz		4	85%	1 : 1
6	R^3 = 4-MePh, R^4 = 4-CN-Bz		4	81%	3.1 : 1
7	R^3 = 1-Naphth, R^4 = Bz		5	81%	5 : 1
8	R^3 = Ph-C≡C, R^4 = Bz		4	92%	5 : 1
9	R^3 = Me, R^4 = Bz		4	85%	2.5 : 1
					
10	R^2 = Ph		4	75%	> 20 : 1
11	R^2 = Ph-C≡C		4	90%	5 : 1
12			12	81%	> 20 : 1
13			12	71%	2.2 : 1

14		12	72%	NA
15		12	40%	> 20 : 1
16		7	75%	> 20 : 1
17		12	76%	NA

R^4 = *p*-CO_2Me-benzoyl

[a]Combined isolated yield. [b]Determined by **^{1}H NMR**. [c]Phenyl vinyl ketone was also isolated as a side product.

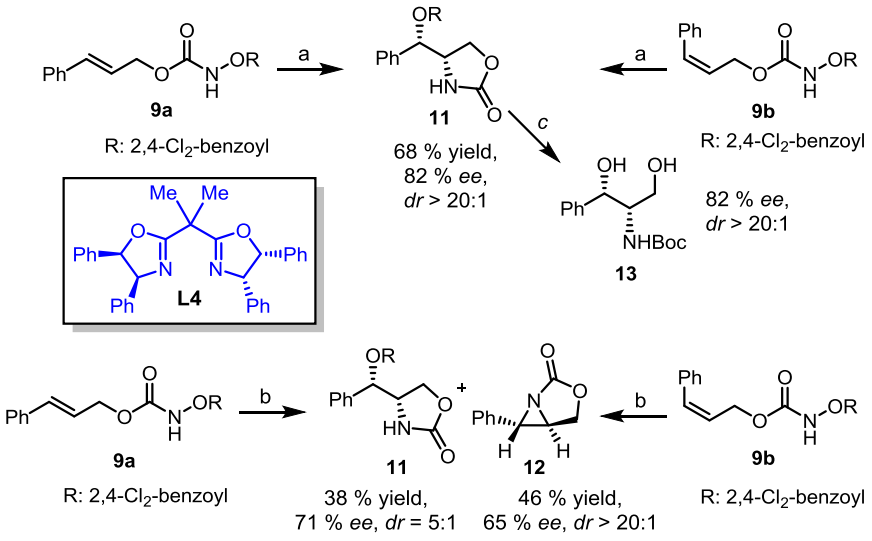
Table 8. Substrate Scope of Iron-Catalyzed Aminohydroxylation

2.3.3 Iron-Catalyzed Asymmetric Aminohydroxylation

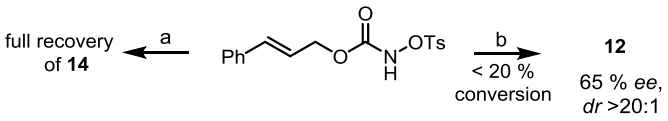
Since the asymmetric synthesis of hydroxyl oxazolidinones by catalytic aminohydroxylation has not been reported, we explored the asymmetric induction with Fe^{II}−chiral bisoxazoline (BOX)[45] complexes (Scheme **35A**). Extensive optimization revealed that $Fe(NTf_2)_2$ −chiral BOX ligand **L4** is effective for enantioinduction. It converts both **9a** and **9b** to *syn*-hydroxyl oxazolidinone **11** with the same *ee* and *dr* (82% *ee*, *dr* > 20:1). More synthetically useful amino alcohol triad **13** was subsequently obtained without stereochemistry erosion with a known method.[40] To our surprise, the diastereoselectivity observed here is different from the one in the $K_4Fe(CN)_6$-catalyzed reaction (Table 3). We also observed that the $Fe(OAc)_2$−chiral BOX ligand **L4** complex catalyzes a convergent aminohydroxylation of both **9a** and **9b**, affording **11** with diminished selectivities (71% *ee*, *dr* = 5:1). In addition to **11**, a chiral aziridine **12** (65% *ee*, *dr* > 20:1) was obtained from both **9a** and **9b**. It is important to note that the sense of enantioinduction for **11** and **12** is the same, and they cannot interconvert under reaction

conditions.[42] We were curious about this reactivity divergence and explored a series of ligands, discovering that the counteranion effect over the product distribution is general. In literature, Bolm demonstrated that $Fe(OTf)_2$−chiral BOX can mediate asymmetric styrene aziridination (up to 40% *ee*). Lebel[37d, 37e] also reported a copper-catalyzed racemic aziridination from tosyl hydroxyl carbamate **14**. To gain further mechanistic insight, we explored the reactivity of 14 under the optimized conditions (Scheme **35B**): $Fe(NTf_2)_2$ is unable to catalyze the cyclization of 14; $Fe(OAc)_2$ can mediate the aziridination of **14**, affording **12** (the same *ee* with the one obtained from **9a** and **9b**), albeit in a low conversion. These results indicate that the $Fe(OAc)_2$-catalyzed aziridination of **9a**, **9b**, and **14** likely go through the same intermediate.

A) convergent enantioselective aminohydroxylation



B) reactivity of tosyl hydroxyl carbamates



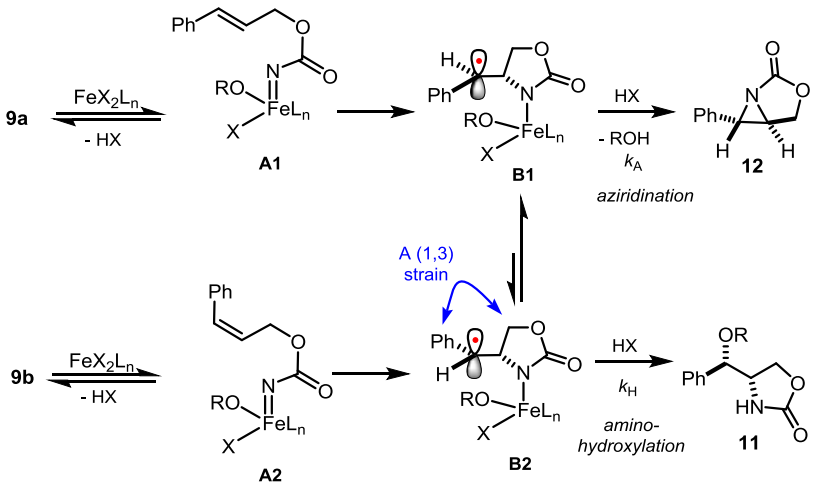
[a]$Fe(NTf_2)_2$ (10 mol %), **10** (20 mol %), MeCN, 0 °C, 8 h. [b]$Fe(OAc)_2$ (10 mol %), **10** (20 mol %), toluene/MeCN = 4:1, 0 °C, 4 h. [c]Boc_2O, Et_3N, DCM, rt, 3 h, then LiOH, dioxane, rt, 4 h, 75% in two steps. Boc_2O = Di-tert-butyl dicarbonate.

.

Scheme 35. Ligand Controlled Asymmetric Induction

2.3.4 Mechanistic Working Hypothesis

The successful asymmetric induction provides further mechanistic insights: (a) Fe^{II}–chiral ligand complexes are involved in both rate- and enantioselectivity-determining steps; (b) olefin aziridination is likely a competing pathway from the same intermediate. Presumably, two distinct types of mechanistic pathways might operate: (a) Kharasch-type atom transfer radical addition[46] or (b) pathways involving iron nitrenoid[47] species. Based on the collected mechanistic evidence, a working hypothesis that best corroborates the $Fe(OAc)_2$-catalzyed enantioselective reaction is shown in **Scheme 33**. First, the $Fe(OAc)_2$–ligand complex can reductively cleave the N–O σ-bond and possibly convert the isomeric *cis*- and *trans*-styrenyl substrates **9a** and **9b** to iron nitrenoids **A1** and **A2**, respectively. Then, a stepwise cycloamination (from **A1** and **A2**) will presumably occur, affording two carbo-radical species, **B1** and **B2** that are in a fast equilibrium. In principle, the intramolecular aziridination should occur much slower than the ligand (OR) transfer from **B2**, because of the unfavorable A (1,3) interaction encountered in the transition state leading to aziridines. In contrast, aziridination can effectively compete with the ligand transfer from **B1**, since the A (1,3) interaction is absent in this conformation. Therefore, the aminohydroxylation should occur predominately from intermediate **B2**, leading to an amino alcohol **11**, while the cyclization from intermediate **B1** will mostly lead to a *trans*-aziridine **12**. It is possible that the mechanistic intricacy will vary with different counterion/ligand combinations, which will influence the relative stability of **B1** vs **B2**, as well as the rates of aziridination (k_A) vs aminohydroxylation (k_H). Since the diastereoselectivity of $K_4Fe(CN)_6$-catalyzed reactions is very different from the ones catalyzed by $Fe(NTf_2)_2$ and $Fe(OAc)_2$, it is less likely this working hypothesis applies for the $K_4Fe(CN)_6$-catalyzed racemic reactions.



Scheme 36. Mechanistic Working Hypothesis

2.4 CONCLUSIONS

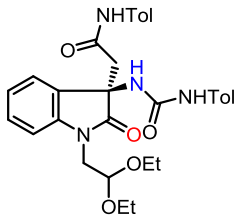
In conclusion, we have discovered a new Fe(II)-catalyzed intramolecular olefin aminohydroxylation with functionalized hydroxylamines, where both the N and O functional groups are efficiently transferred for olefin aminohydroxylation. Preliminary mechanistic studies revealed that an iron nitrenoid is possibly an intermediate that can undergo either olefin aziridination or aminohydroxylation. This discovery opens up the possibility of developing a unique and general approach for stereoselective olefin amination. Our current effort focuses on better understanding the mechanistic details of this process and its application in complex molecule synthesis.

3 CHAPTER III IRON(II)-CATALYZED ASYMMETRIC INTRAMOLECULAR AMINOHYDROXYLATION OF INDOLES

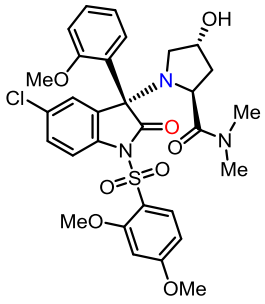
3.1 INTRODUCTION

3.1.1 Naturally Occurring Molecules

Indole chemistry has been extensively explored since its first synthesis by Baeyer *et al* in 1866. Due to its prevalence in the structures of numerous medicinal agents and biologically active natural products, the study of indole chemistry remains to be appealing in constructing those important indole alkaloids as depicted in Figure **4**, such as AG-041R, a gastrin/CCK-B receptor agonist; SSR-149415, also called Nalivaptan, a medicine for the treatment of anxiety and depression;[48] and natural products psychotrimine, kapakahines, and chaetomin.[49] More interestingly, all of these natural products are bearing either amino oxindoles or amino indolanes structural motifs. Much attention has been focused on those well-established reactions, such as oxidative (radical) dimerization, or electrophilic cyclization cascades. However, methodologies for diastereo- and enantioselectively catalytic functionalization at the C2 and C3 positions for the synthesis of amino oxindoles and amino indolanes are less explored.



AG-041R



Nelivaptan

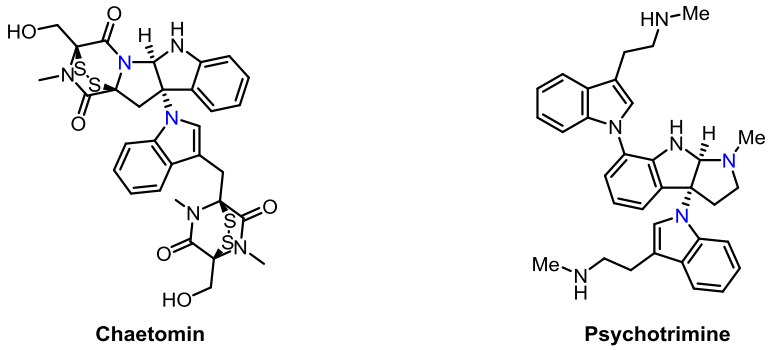
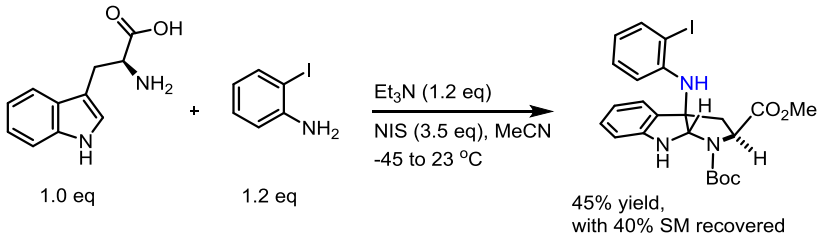


Figure 4. Amino Oxindoles and Amino Indolanes Structural Motifs

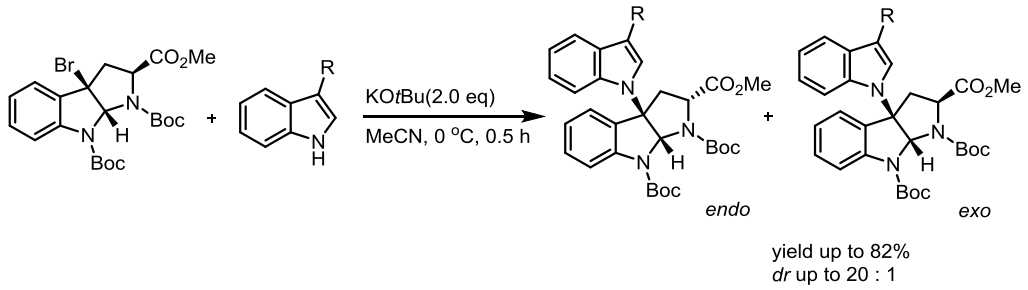
3.1.2 Chiral Substrate-Controlled C(3)-N(1') Coupling

Chiral substrate-controlled indole–aniline coupling and stereospecific functional group manipulation are among the strategies that have been applied to the asymmetric synthesis of 3-amino indolanes. Phil S. Baran[49b] demonstrated a powerful and exceptionally concise gram scale synthesis of Psychotrimine with minimal use of protection chemistry and redox steps. The proposed coupling reaction was explored using 2-Iodoaniline and L-tryptophan (Scheme **37**) with a variety of oxidants. Most oxidants afforded a complex mixing system. With exceptionally simple halogenating agents such as NCS and NBS, the cyclized C(3)-N(1′) coupling product was furnished as the major diastereomer. The key finding in making the reaction robust and scalable was using NIS to afford the C3 aminated product in 45% isolated yield along with 40% starting material recovered.



Scheme 37. Total Synthesis of Psychotrimine

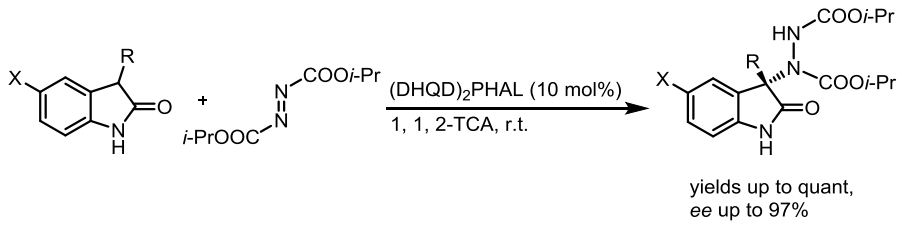
Meanwhile, Rainier[49a] disclosed another C(3)-N(1′) heterodimeric indolines synthesis. Luckily they achieved 28% yield desired product for their first batch as a single diastereoisomer. Interestingly, the reaction product bearing a methyl ester functional group could epimerize from the *exo*-position to the thermodynamically more favorable *endo*-position. Thus, a novel and facile entry into the C(3)-N(1′) construction with up to 82% yield for 8 examples and up to 20:1 *dr* were thus reported.



Scheme 38. The Synthesis of C(3)-N(1') Dimers

3.1.3 Organic Molecules and Lewis Acid-Catalyzed Reactions

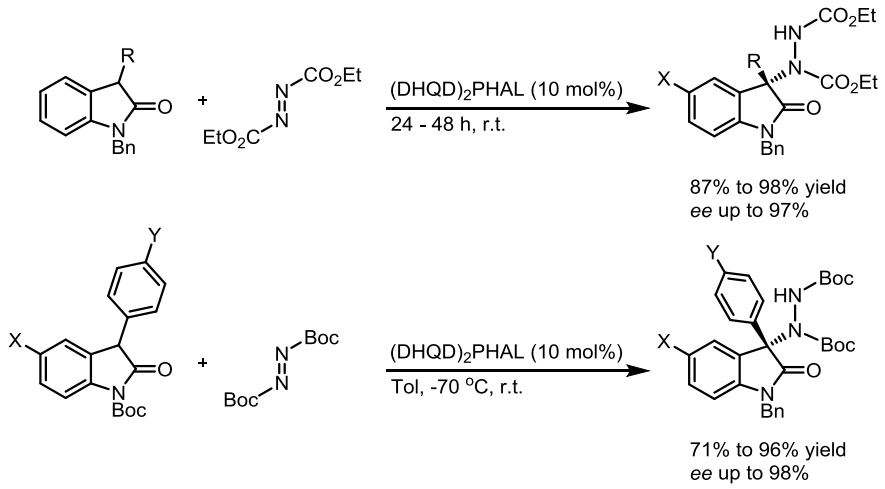
An effective approach for the enantio-synthesis of 3-amino-2-oxindoles was discovered by Yongjun Chen.[50] Biscinchona alkaloids catalyzed asymmetric amination of unprotected oxindoles with the generation of quaternary chiral carbon center was thus realized by the employment of azodicarboxylate as the nitrogen source.



Scheme 39. Organocatalytic Amination of 2-Oxindoles

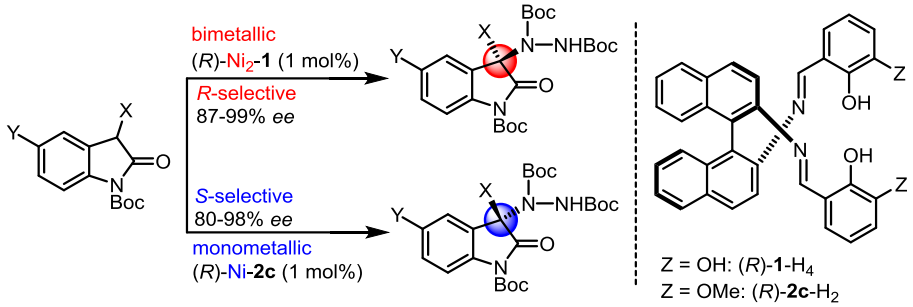
Another enantioselective α-amination of aryl oxindoles catalyzed by cinchona alkaloids has been developed by Carlos and coworkers.[51] The reaction is general, broad in substrate scope,

and affords the desired products in good yields with good to excellent enantioselectivities. This study provides a general organocatalytic method for the creation of nitrogen-containing, tetrasubstituted chiral centers at the C3 position of alkyl and aryl oxindoles.



Scheme 40. Expanded Substrate Scope for Amination of 2-Oxindoles

Recently, a highly enantioselective catalytic synthesis of 3-aminooxindoles with a tetrasubstituted carbon stereocenter is reported by Shibasaki's group.[52] 1−2 mol % of homo bimetallic (*R*)-Ni_2−Schiff base can catalyze the asymmetric amination of 3-substituted oxindoles with azodicarboxylates to give (*R*)-products in 89 to 98% yield and with large than 87% *ee*. While reversed *ee* was observed when switching to monometallic Schiff base complexes without loss of yield and *ee*. A formal synthesis of the key intermediate for AG-041R from an optically active oxindole is also described.



Scheme 41. Catalytic Asymmetric Synthesis of 3-Aminooxindoles

Dr. Xiaoming Feng also made a great contribution in this area during the last few years.[53] They demonstrated that C2-symmetric N,N'-dioxide amide compounds (as shown in Figure **5**)are effective in a variety of chiral ligand metal-catalyzed or organocatalyzed asymmetric reactions under mild reaction conditions. Due to the easy accessibility, extensive versatility, as well as other advantages, such as excellent enantioselectivity and reactivity, low price, operational simplicity, mild reaction conditions, thus their applications in both traditional and new catalytic asymmetric reactions, are promising.

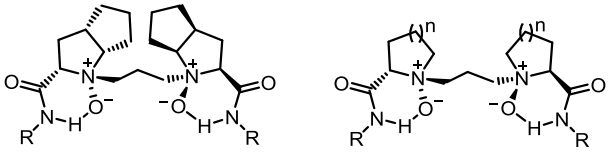
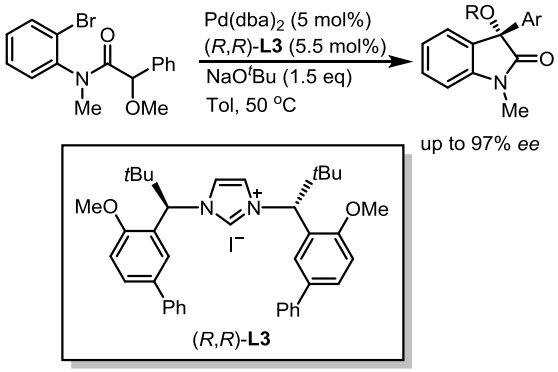


Figure 5. Chiral N,N'-Dioxides

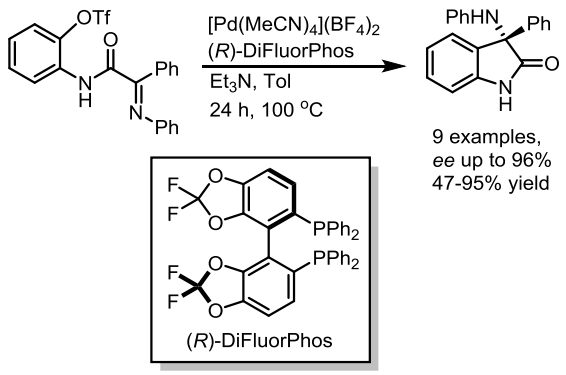
3.1.4 Intramolecular α-Arylation of Amides

Peter Kundig developed an asymmetric Pd/NHC-catalyzed intramolecular α-arylation of amide enolates to afford optically active 3-alkoxy or 3-aminooxindoles in high yields and enantioselectivities.[54]



Scheme 42. Chiral NHC Carbene Catalyzed Oxindole Synthesis

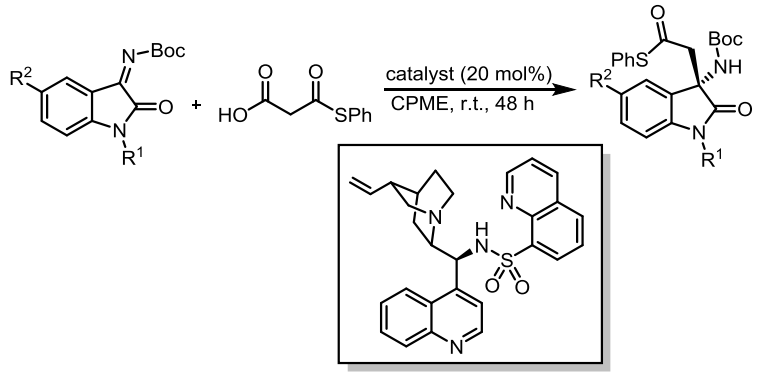
Recently, Steven Ley reported an approach for enantioselective 3-amino-2-oxindoles through a Pd-catalyzed intramolecular arylation of α-ketimino amides using chiral phosphine ligand.[55]



Scheme 43. Pd-Mediated Asymmetric Intramolecular Arylation of Ketimino Amides

3.1.5 Organic Molecule-Catalyzed Additions

More interestingly, a highly enantioselective decarboxylative addition of MAHTs to ketimines derived from isatins by using novel cinchonidine organocatalysts is described by Norio Shibata in 2012.[56] In the paper, they claimed the first example of decarboxylative addition of MAHTs to ketimines, while the afforded product could be further converted to optically active (+)-AG-041R.

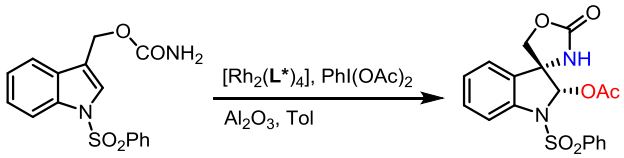


Scheme 44. Decarboxylative Addition of MAHT to Ketimines

3.1.6 Rhodium-Catalyzed Intramolecular Aminohydroxylation of Indoles or Pyrroles

Despite these key discoveries, a method that can provide both amino oxindoles and amino indolanes with synthetically useful *ee* through catalytic asymmetric indole aminohydroxylation has yet to be discovered. Inspired by the pioneering Sharpless asymmetric aminohydroxylation,[15] there has been significant progress in the development of methods for selective olefin aminohydroxylation as we discussed in chapter 2.[16a, 16g, 17-18, 19a-c, 21, 23-24, 26, 29, 33-34] Albert Padwa[27] and co-work came up with the iodine (III)-mediated aziridination reaction of an indolyl-substituted carbamate which requires a Rh(II) catalyst and proceeds by metallonitrene intermediate. A metal-free zwitterion is generated by stepwise addition across the indole π-bond followed by Rh (II) detachment, which ultimately furnishes the final products, as demonstrated in Scheme **23**.

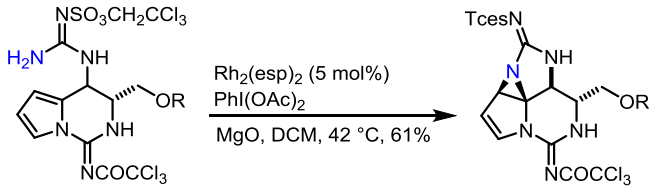
Chi-ming Che[57] has found a mild and straightforward enantioselective method for the synthesis of optically active indole oxazolidine. Chiral dirhodium complexes can catalyze the asymmetric intramolecular aziridination of unsaturated sulfonamides and carbamates giving excellent yield and moderate *ee*. The forming aziridine can be opened in the presence of other nucleophiles, such as acetate. Their efforts are currently underway to improve the moderate to good *ee*.



Scheme 45. Intramolecular Aziridination and Nucleophilic Ring-Opening

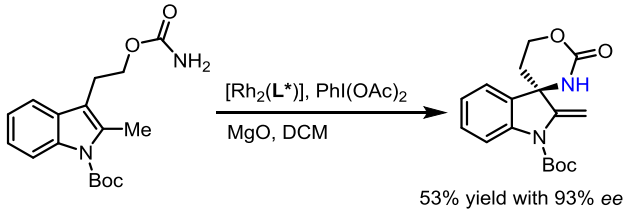
In a stereoselective total synthesis of (+)-Gonyautoxin 3 reported by J. Du Bois[58] in 2008. This important transformation capitalized on the novel reactivity of Rh-bound guanidine nitrene

that is capable of modifying both C-H bond and π system to afford the pyrrole amination product.



Scheme 46. Synthesis of (+)-Gonyautoxin 3

Recently, Iwabuchi disclosed a chiral Rh-nitrenoid species based oxidative nitrogen atom transfer reaction, with a versatile and highly enantioselective synthesis of spiro-*β*-lactam cores and expanded the substrate scope. The further effort towards the total synthesis of chartelline alkaloids is now ongoing in his lab.[59]

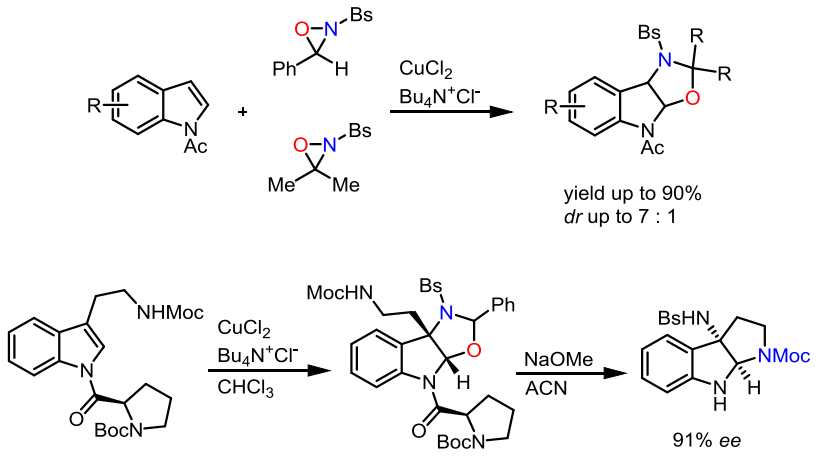


Scheme 47. Rh-Mediated Intramolecular Aza-spiroannulation

3.1.7 Previous Indole Aminohydroxylation Reactions

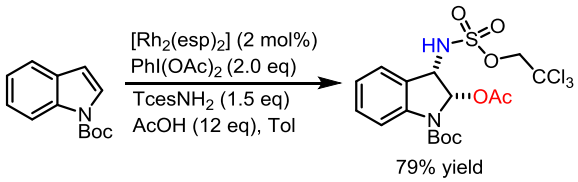
Y oon has been interested in developing a synthetic methodology for rapid constructing a class of pyrroloindoline alkaloids, aiming at C-N bond formation in an enantioselective fashion. Later on, they have demonstrated that the copper (II)-catalyzed intermolecular oxyamination of indoles affords aminals in high yields and with excellent regioselectivity.[18e] Based on the knowledge of their recently revised mechanistic model,[35] a radical intermediate is consistent with the furnished high regioselective products that can be easily transformed into 3-aminoindoles, indolines, pyrroloindolines and other synthetically valuable heterocyclic building blocks. Finally, by incorporation of a chiral auxiliary, they subsequently achieved asymmetric oxyamination of

tryptamine derivatives. This transformation enables the enantioselective construction of 3-aminopyrroloindolines that is useful in the synthesis of oxidized-indole natural products.



Scheme 48. Oxaziridine-Mediated Oxyamination of Indoles

M ore recently, Dauban[60] utilized this rhodium nitrene for direct nitrogen atom transfer to indolic derivatives. This efficient intermolecular oxyamidation reaction affords access to 2,3-substituted indolines. Interestingly, its stereoselectivity is controlled by the nucleophile, while the regioselectivity is operated by the introduction of a substituent at C3. Moreover, the introduction of nitrogen nucleophiles enables the development of the catalytic diamination of indoles.



Scheme 49. Catalytic Oxyamidation of Indoles

3.2 EXPERIMENT

3.2.1 General Procedures

General Procedures. All reactions were performed in oven-dried or flame-dried round-bottom flasks and vials. Stainless steel syringes and cannula were used to transfer air- and moisture-sensitive liquids. Flash chromatography was performed using silica gel 60 (230-400 mesh) from Sigma-Aldrich.

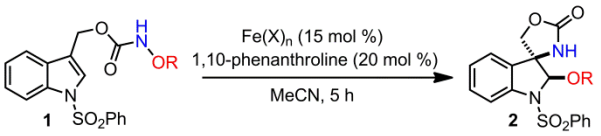
Materials. Commercial reagents were purchased from Sigma-Aldrich, Fluka, EM Science, and Lancaster and used as received. All solvents were used after being freshly distilled unless otherwise noted.

Instrumentation. Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Bruker UltraShield-400 (400 MHz). Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to the NMR solvent residual peak ($CHCl_3$: δ 7.26; DMSO: δ 2.50). Chemical shifts for carbons are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$: δ 77.0; DMSO: δ 39.5). Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet), coupling constants (*J*) in Hertz (Hz), and integration.

The mass spectroscopic data were obtained at the Georgia State University mass spectrometry facility using a Micromass Platform II single quadrupole instrument. Infrared (IR) spectra were obtained by using a Perkin Elmer Spectrum 100 FT-IR spectrometer. Data are represented as follows: frequency of absorption (cm^{-1}).Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Perkin Elmer model 343 at 589 nm, and are reported as [α

]$_D$ (concentration ingrams/100 mL solvent). Chiral HPLC analysis was performed with an Agilent HPLC instrument.

Abbreviations used: EtOH–ethanol, EtOAc–ethyl acetate, THF–tetrahydrofuran, MeOH–methanol, Et2O–diethyl ether, CH2Cl2–dichloromethane, TEA–triethylamine, MeCN–acetonitrile, MS–molecular sieves, CDI–1,1′-carbonyldiimidazole, Troc–2,2,2-trichloroethoxycarbonyl, DCC–N,N′-dicyclohexylcarbodiimide, TLC–thin layer chromatography ，Boc_2O–di-tert-butyl dicarbonate, DMAP−4-dimethylaminopyridine.

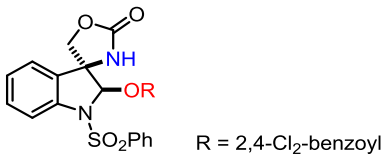


entry[a]	$Fe(X)_n$	R	T (°C)	conversion[b]	yield[c]
1	$K_4Fe(CN)_6$	Me	70	<5%	<5%
2	$K_4Fe(CN)_6$	Ts	70	35%	<5%
3	$K_4Fe(CN)_6$	Bz	70	61%	44%
4	$Fe(OTf)_2$	Bz	23	79%	39%
5	$Fe(OTf)_2$	4-CO_2Me-benzoyl	23	>95%	53%
6	$Fe(OTf)_2$	2,4-Cl_2-benzoyl	23	>95%	72%
7	$Fe(NTf_2)_2$	2,4-Cl_2-benzoyl	23	>95%	74%
8	$FeCl_2$	2,4-Cl_2-benzoyl	23	>95%	63%
9	$FeBr_2$	2,4-Cl_2-benzoyl	23	>95%	51%
10	$Fe(OAc)_2$	2,4-Cl_2-benzoyl	23	>95%	76%
11	$FeSO_4$	2,4-Cl_2-benzoyl	23	>95%	86%

Table 9. Catalyst Discovery for the Racemic Indole Aminohydroxylation

G eneral Procedure: To a flame-dried vial were added $Fe(X)_n$ (0.007 mmol) and 1,10-phenanthroline (0.014 mmol). After evacuation upon oil pump and refill with argon three times, anhydrous and degassed MeCN (1.5 mL) was added. The resulting suspension was stirred vigorously at room temperature for 30 min; substrate **1** (0.04 mmol) in MeCN (0.5 mL) was added afterwards. The reaction was stirred at the indicated temperature for 5 h. Conversions were determined by ^{1}H NMR analysis with 1, 3, 5-trimethoxybenzene as an internal standard. The reaction was quenched with saturated $NaHCO_3$ aqueous solution, and extracted with DCM three times. The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*.

The residue was purified by silica gel flash column (hexane:THF = 4:1) to afford the racemic aminohydroxylation product **2**.



2

(±)-2'-Oxo-1-(phenylsulfonyl)spiro[indoline-3,4'-oxazolidine]-2-yl 2,4-dichlorobenzoate (2): ^{1}H NMR (400 MHz, d_6-DMSO, ppm): δ 8.80 (s, 1H), 8.02 (d, J = 7.6 Hz, 2H), 7.84 (s, 1H), 7.77 (d, J = 8.4 Hz, 1H)， 7.69 (t, J = 6.8 Hz, 1H), 7.57-7.54 (m, 3H), 7.49 (d, J = 6.8 Hz, 1H), 7.41 (s, 2H), 7.21 (s, 1H), 6.99 (s, 1H), 4.62 (d, J = 9.2 Hz, 1H), 4.06 (d, J = 8.8 Hz, 1H);^{13}C NMR (100 MHz, d_6-DMSO, ppm): δ 162.7, 158.1, 150.4, 139.5, 138.7, 138.0, 134.9, 134.8, 133.7, 131.4, 131.2, 130.2, 129.7, 128.0, 127.7, 127.0, 125.7, 125.4, 113.5, 89.4, 73.9, 67.0; IR ν_{max} (neat)/cm^{-1}: 3443 (w), 1768 (s), 1238 (m), 1029 (m); HRMS (ESI) calcd for $C_{23}H_{15}Cl_2N_2O_6S$ $[M-H]^-$: 517.0028, found 517.0042.

3.2.2 General Synthetic Route for Substrates Preparation and Characterization

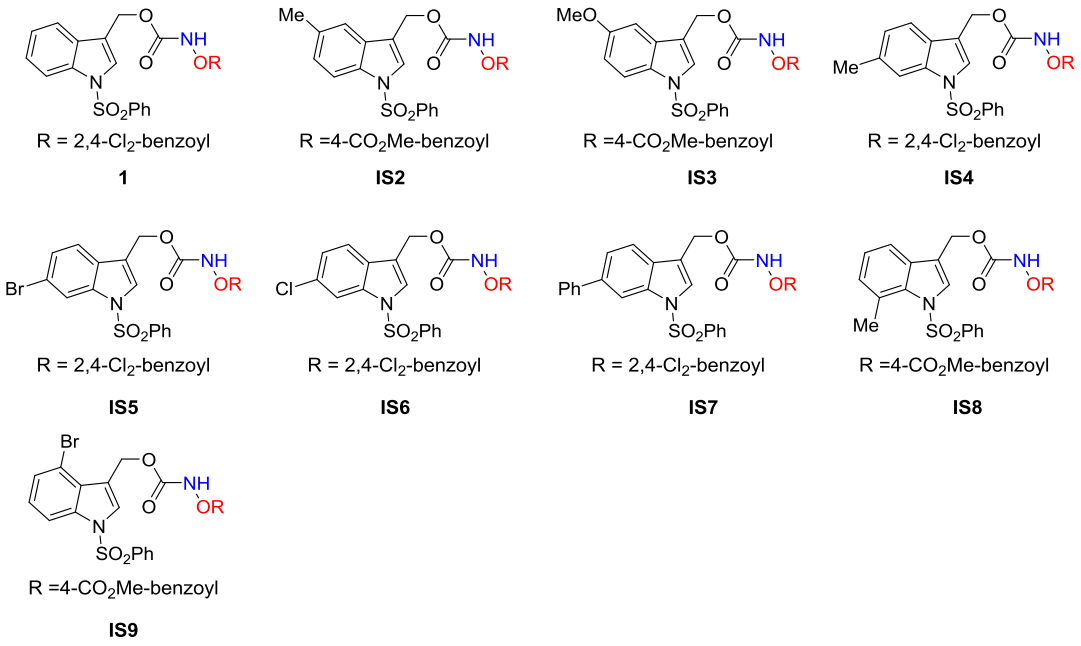
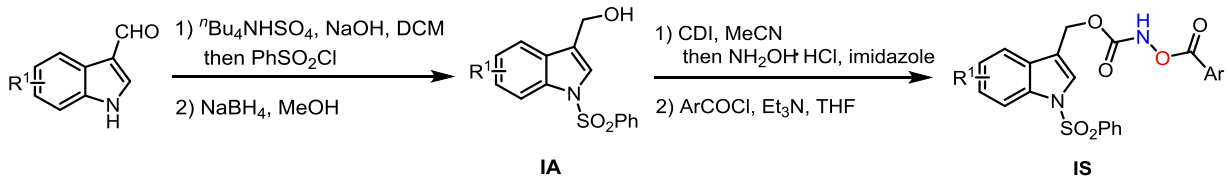


Table 10. Substrate Scope

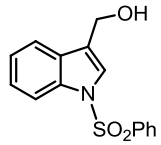


Scheme 50. General Synthetic Route for Substrates Preparation

3.2.2.1 Preparation of Indole Alcohols and Product Characterization

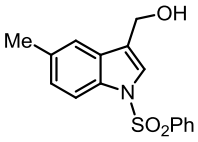
G eneral Procedure for Preparation of Indole Alcohols (IA):[61] At 0 °C, to a solution of indole aldehyde (1 mmol) in DCM (10 mL), was added $^{n}Bu_4NHSO_4$ (0.05 mmol, 17 mg) and NaOH (1.1 mmol, 44 mg) subsequently. After stirring for 0.5 h at 0 °C, $PhSO_2Cl$ (1.1 mmol, 194 mg) was added dropwise and stirred for additional 0.5 h at room temperature. Then the reaction mixture was diluted with DCM (50 mL) and water (50 mL). The organic layer was separated and the aqueous phase was extracted with 50 mL DCM. The combined organic layer

was washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo.* The crude product was purified with flash silica gel column chromatography (20% EtOAc in hexanes) to afford the protected indole aldehyde (75–95% yield). To a solution of protected indole aldehyde obtained (1 mmol) in methanol (10 mL), $NaBH_4$ (1.1 mmol, 41 mg) was added in one portion at 0 °C. After stirring for 30 min, the solvents were removed under vacuum, and the residue was extracted by DCM (50 mL). The organic layer was washed by brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel flash column chromatography (40% EtOAc in hexanes) to afford the indole alcohol (**IA1–IA9**, 85–95% yield).



IA1

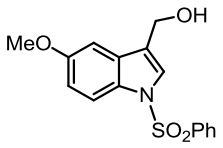
(1-(Phenylsulfonyl)-1H-indol-3-yl)methanol (**IA1**): **IA1** was prepared by following the literature procedure and the NMR spectra were in accordance with the previously reported data.[61]



IA2

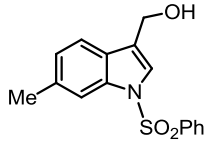
(5-Methyl-1-(phenylsulfonyl)-1H-indol-3-yl)methanol (**IA2**)**:** white solid, mp: 119–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.87–7.84 (m, 3H), 7.48–7.44 (m, 2H), 7.38–7.35 (m, 3H), 7.14 (d, J = 8.4 Hz, 1H), 4.72 (s, 2H), 2.38 (s, 3H), 2.28 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 138.0, 133.7, 133.6, 133.0, 129.6, 129.1, 126.6, 126.3, 123.7, 122.4, 119.7,

113.2, 56.9, 21.2; IR ν_{max} (neat)/cm^{-1}: 3323 (w), 1447 (m), 1364 (m), 1172 (s), 1118 (s); HRMS (ESI) calcd for $C_{16}H_{14}NO_3S$ $[M-H]^-$: 300.0704, found 300.0694.



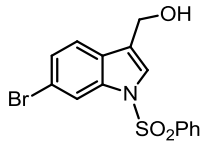
IA3

(5-Methoxy-1-(phenylsulfonyl)-1H-indol-3-yl)methanol(IA3): white solid, mp: 105–107 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.79 (d, J = 8.0 Hz, 2H), 7.45 (s, 1H), 7.40 (t, J = 7.2 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 6.96 (s, 1H), 6.90 (d, J = 9.2 Hz, 1H), 4.66 (s, 2H), 3.72 (s, 3H), 2.85 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 156.3, 137.7, 133.6, 130.4, 129.8, 129.0, 126.4, 124.2, 122.7, 114.3, 113.9, 102.2, 56.6, 55.4; IR ν_{max} (neat)/cm^{-1}: 3403 (w), 1475 (m), 1366 (m), 1170 (s), 1029 (s); HRMS (ESI) calcd for $C_{16}H_{14}NO_4S$ $[M-H]^-$: 316.0644, found 316.0649.



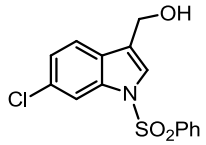
IA4

(6-Methyl-1-(phenylsulfonyl)-1H-indol-3-yl)methanol (**IA4):** white solid, mp: 118-120 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.86 (d, J = 8.0 Hz, 2H), 7.80 (s, 1H), 7.51-7.38 (m, 5H), 7.06 (d, J = 8.0 Hz, 1H), 4.73 (s, 2H), 2.47 (s, 3H), 2.07 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 138.2, 135.8, 135.2, 133.7, 129.2, 127.1, 126.6, 124.9, 123.0, 122.5, 119.4, 113.7, 57.0, 21.9; IR ν_{max} (neat)/cm^{-1}: 3352 (w), 1448 (m), 1367 (m), 1275 (s), 1173 (s); HRMS (ESI) calcd for $C_{16}H_{14}NO_3S$ $[M+H]^+$: 300.0704, found 300.0694.



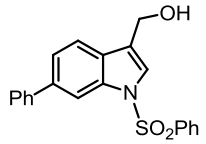
IA5

(6-Bromo-1-(phenylsulfonyl)-1H-indol-3-yl)methanol (**IA5):** white solid, mp: 124-126 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.16 (s, 1H), 7.87 (d, J = 7.6 Hz, 2H), 7.55 (t, J = 7.2 Hz, 1H), 7.49-7.43 (m, 4H), 7.34 (d, J = 8.4 Hz, 1H), 4.76 (s, 2H), 1.90 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 137.9, 136.0, 134.1, 129.5, 128.2, 126.7, 124.0, 122.3, 121.1, 118.8, 116.6, 56.9; IR ν_{max} (neat)/cm^{-1}: 3370 (w), 1367 (m), 1276 (s), 1174 (s), 1125 (s); HRMS (ESI) calcd for $C_{15}H_{11}NO_3SBr$ [M-H]$^-$: 363.9643, found 363.9645.



IA6

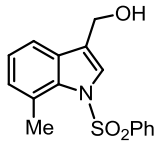
(6-Chloro-1-(phenylsulfonyl)-1H-indol-3-yl)methanol(**IA6):** white solid, mp: 141–143 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.03 (s, 1H), 7.91 (d, J = 8.0 Hz, 2H), 7.59 (t, J = 7.2 Hz, 1H), 7.54-7.47 (m, 4H), 7.25 (d, J = 8.4 Hz, 1H), 4.81 (d, J = 4.4 Hz, 2H), 1.73 (t, J = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 137.9, 135.8, 134.1, 131.2, 127.9, 126.8, 124.1, 122.2, 120.8, 113.9, 57.0; IR ν_{max} (neat)/cm^{-1}: 3366 (w), 1448 (m), 1370 (m), 1173 (s), 1132 (s); HRMS (ESI) calcd for $C_{15}H_{11}NO_3SCl$ [M-H]$^-$: 320.0148, found 320.0146.



IA7

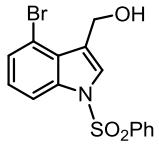
(6-Phenyl-1-(phenylsulfonyl)-1H-indol-3-yl)methanol(IA7): ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.26 (s, 1H), 7.92 (d, J = 7.6 Hz, 2H), 7.67–7.60 (m, 4H), 7.50–7.48 (m, 4H),

7.43–7.39 (m, 3H), 4.81 (s, 2H), 2.27 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 141.2, 138.6, 138.1, 136.1, 134.0, 129.4, 128.9, 128.7, 127.5, 127.4, 126.8, 124.1, 123.1, 122.6, 120.2, 112.1, 57.0; IR ν_{max} (neat)/cm^{-1}: 3371 (w), 1369 (m), 1174 (s), 1122 (m); HRMS (ESI) calcd for $C_{21}H_{16}NO_3S$ $[M-H]^-$: 362.0851, found 362.0859.



IA8

(7-Methyl-1-(phenylsulfonyl)-1H-indol-3-yl)methanol(IA8): white solid, mp: 118–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.66 (s, 1H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.47–7.40 (m, 3H), 7.15 (t, *J* = 7.2 Hz, 1H), 7.04 (d, *J* = 7.2 Hz, 1H), 4.82 (s, 2H), 2.51 (s, 3H), 2.06 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 139.8, 135.4, 133.5, 131.5, 129.3, 128.6, 127.2, 126.3, 125.0, 123.9, 121.6, 117.6, 57.0, 21.6; IR ν_{max} (neat)/cm^{-1}: 3361 (w), 1447 (m), 1354 (s), 1275 (s), 1083 (s); HRMS (ESI) calcd for $C_{16}H_{15}NO_3SNa$ $[M+Na]^+$: 324.0670, found 324.0670.

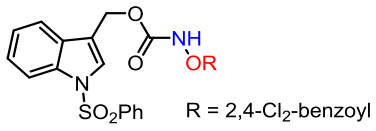


IA9

(4-Bromo-1-(phenylsulfonyl)-1H-indol-3-yl)methanol (IA9): ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.98 (d, *J* = 6.4 Hz, 2H), 7.73 (s, 1H), 7.69 (t, *J* = 7.2 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.25 (t, *J* = 8.0 Hz, 1H), 5.31 (t, *J* = 5.2 Hz, 1H), 4.86 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 136.7, 135.9, 134.8, 129.9, 127.8, 127.4, 126.7, 126.1, 124.9, 113.7, 112.7, 56.3; IR ν_{max} (neat)/cm^{-1}: 3006 (w), 1276 (m), 1173 (w), 978 (w), 750 (s); HRMS (ESI) calcd for $C_{15}H_{12}NO_3SBrNa$ $[M+Na]^+$: 387.9619, found 387.9626.

3.2.2.2 Preparation of Indole Hydroxylamines and Product Characterization

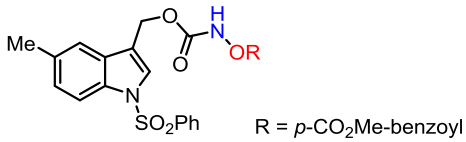
G eneral Procedure for Preparation of Indole Substrates (IS): To a solution of indole alcohol (1 mmol) in MeCN (10 mL), was added CDI·HCl (3 mmol, 599 mg) at room temperature. After stirring for 1.0 h, NH_2OH·HCl (4 mmol, 278 mg), imidazole (5 mmol, 340 mg) were added subsequently and stirred for an additional 4 h at room temperature. Then the reaction mixture was diluted with DCM (50 mL) and water (50 mL). The organic layer was separated and aqueous phase was extracted with 30 mL DCM three times. The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified with silica gel flash column chromatography (50% EtOAc in hexanes) to afford the hydroxyl carbamate product (70–85% yield). To a solution of indole hydroxyl carbamate (1.0 mmol) and TEA (1.5 mmol, 152 mg) in THF (10 mL), 2, 4-dichlorobenzoyl chloride (1.05 mmol, 218 mg) in THF (3.0 mL) was added dropwise at 0 °C. After stirring for 1 h, the mixture was quenched by cautiously adding water (0.2 mL). Then the reaction mixture was diluted with DCM (50 mL) and water (50 mL). The aqueous phase was extracted with DCM (50 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified with silica gel flash column chromatography (30% EtOAc in hexanes) to afford the indole substrates (**1** to **IS9**) (75–95% yield).



1

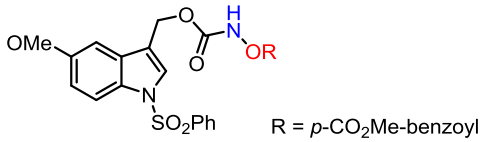
(1-(Phenylsulfonyl)-1H-indol-3-yl)methyl 2,4-dichlorobenzoyloxycarbamate (1) : white solid, mp: 165–167 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.53 (brs, 1H), 7.99 (d, J =

8.4 Hz, 1H), 7.90 (d, *J* = 7.6 Hz, 2H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.70 (s, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.54–7.41 (m, 4H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.27–7.23 (m, 2H), 5.39 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 163.6, 156.2, 139.8, 137.9, 135.6, 135.0, 133.9, 132.7, 131.2, 129.3, 129.2, 127.2, 126.8, 126.1, 125.2, 124.5, 123.6, 119.6, 116.5, 113.6, 60.0; IR ν_{max} (neat)/cm^{-1}: 3006 (w), 1747 (s), 1585 (m), 1447 (s), 1374 (m), 1275 (s), 1085 (s); HRMS (ESI) calcd for $C_{23}H_{15}Cl_2N_2O_6S$ [M-H]$^-$: 517.0028, found 517.0025.



IS2

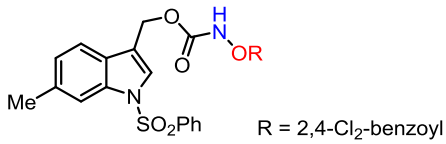
Methyl 4-((((5-methyl-1-(phenylsulfonyl)-1H-indol-3-yl) methoxy) carbonylaminooxy) carbonyl) benzoate (IS2): white solid, mp: 121-122 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.41 (s, 1H), 8.12 (s, 4H), 7.88–7.84 (m, 3H), 7.62 (s, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.33 (s, 1H), 7.15 (d, *J* = 8.4 Hz， 1H), 5.35 (s, 2H), 3.96 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 165.0, 156.2, 138.1, 135.1, 134.0, 133.4, 133.36, 130.3, 129.9, 129.8, 129.5, 129.4, 126.8, 126.7, 126.3, 119.5, 116.4, 113.4, 60.2, 52.7, 21.3; IR ν_{max} (neat)/cm^{-1}:3266 (w), 1721 (s), 1448 (m), 1370 (m), 1226 (s), 1095 (s); MS(ESI) $C_{26}H_{21}N_2O_8S$ [M-H]$^-$: 521.1.



IS3

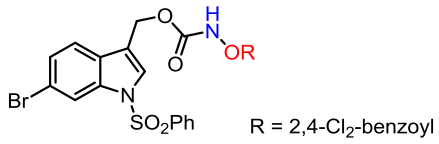
Methyl 4-((((5-methoxy-1-(phenylsulfonyl)-1H-indol-3-yl) methoxy) carbonylaminooxy) carbonyl) benzoate(IS3): white solid, mp: 122–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.37 (s, 1H), 8.11 (s, 4H), 7.87–7.85 (m, 3H), 7.62 (s, 1H), 7.53 (t, *J* = 7.2

Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 6.98 (s, 1H), 6.94 (d, *J* = 9.2 Hz, 1H), 5.35 (s, 2H), 3.96 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 166.0, 165.2, 156.8, 156.3, 138.1, 135.3, 134.1, 130.3, 129.4, 128.3, 126.9, 116.7, 114.8, 114.6, 102.0, 60.2, 55.8, 52.8; IR ν_{max} (neat)/cm^{-1}: 3111 (w), 1718 (s), 1450 (m), 1376 (m), 1216 (s), 1097 (s); MS(ESI) $C_{26}H_{21}N_2O_{69}S$ $[M-H]^-$: 537.0.



IS4

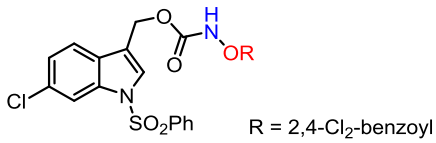
(6-Methyl-1-(phenylsulfonyl)-1H-indol-3-yl)methyl 2,4-dichlorobenzoyloxycarbamate(IS4): white solid, mp: 144–146 °C; ^{1}H NMR (400 MHz, d_6-DMSO, ppm): δ 11.52 (brs, 1H), 7.99 (d, *J* = 7.2 Hz, 2H), 7.88-7.77 (m, 4H), 7.68 (t, *J* = 6.8 Hz, 1H), 7.60-7.49 (m, 4H), 7.09 (d, *J* = 7.2 Hz, 1H), 5.34 (s, 2H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO, ppm): δ 163.3, 156.2, 138.5, 137.0, 135.0, 134.8, 133.9, 132.6, 130.8, 129.9, 127.9, 126.9, 126.7, 125.8, 125.6, 125.0, 119.8, 117.4, 113.1, 58.9, 21.5; IR ν_{max} (neat)/cm^{-1}: 3006 (w), 2250 (w), 1275 (s), 1025 (s), 820 (s); HRMS (ESI) calcd for $C_{24}H_{17}Cl_2N_2O_8S$ $[M-H]^-$: 531.0184, found 531.0180.



IS5

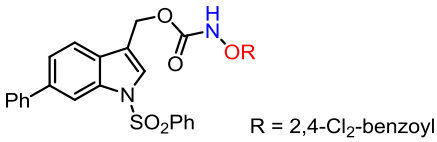
(6-Bromo-1-(phenylsulfonyl)-1H-indol-3-yl)methyl 2,4-dichlorobenzoyloxycarbamate(IS5): white solid, mp: 139–141 °C; ^{1}H NMR (400 MHz, d_6-DMSO, ppm): δ 11.53 (s, 1H), 8.08 (s, 1H), 8.03–8.00 (m, 3H), 7.82 (s, 2H), 7.72 (t, *J* = 7.6 Hz, 1H), 7.64–7.55 (m, 4H), 7.45 (d, *J* = 8.0 Hz, 1H), 5.35 (s, 2H); ^{13}C NMR (100 MHz, d_6-DMSO,

ppm): δ 163.2, 156.1, 138.5, 136.7, 135.04, 135.0, 133.9, 132.6, 130.8, 130.1, 128.2, 127.9, 127.3, 126.7, 125.5, 122.1, 118.0, 117.4, 115.6, 58.6; IR ν_{max} (neat)/cm^{-1}: 3006 (w), 2251 (w), 1276 (s), 1025 (s), 820 (s); HRMS (ESI) calcd for $C_{23}H_{14}BrCl_2N_2O_8S$ $[M-H]^-$: 594.9133, found 594.9124.



IS6

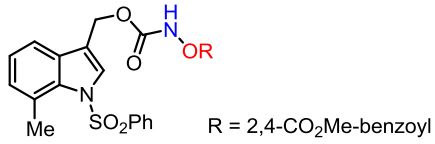
(6-Chloro-1-(phenylsulfonyl)-1H-indol-3-yl)methyl 2,4-dichlorobenzoyloxycarbamate(IS6): white solid, mp: 160–162 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.51 (s, 1H), 7.97 (s, 1H), 7.88 (d, J = 7.6 Hz, 2H), 7.82 (d, J = 8.4 Hz, 1H), 7.65 (s, 1H), 7.55 (t, J = 7.2 Hz, 1H), 7.27 (s, 4H), 7.26 (d, J = 5.2 Hz， 1H)， 7.18 (d, J = 8.0 Hz, 1H), 5.33 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 163.6, 156.1, 140.0, 137.6, 135.7, 135.3, 134.2, 132.7, 131.3, 131.2, 129.5, 127.6, 127.2, 126.8, 126.6, 124.4, 124.3, 120.6, 116.4, 113.7, 59.7; IR ν_{max} (neat)/cm^{-1}: 3005 (w), 1752 (s), 1585 (m), 1448 (m), 1375 (s), 1275 (s), 1095 (s); HRMS (ESI) calcd for $C_{23}H_{14}Cl_3N_2O_7S$ $[M-H]^-$: 550.9638, found 550.9646.



IS7

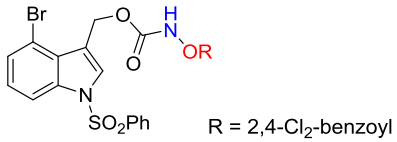
(6-Phenyl-1-(phenylsulfonyl)-1H-indol-3-yl)methyl 2,4-dichlorobenzoyloxycarbamate (IS7): ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.39 (s, 1H), 8.22 (s, 1H), 7.94 (d, J = 7.6 Hz, 2H), 7.88 (d, J = 8.4 Hz, 1H), 7.72 (s, 1H), 7.65–7.63 (m, 3H), 7.58–7.32 (m, 8H), 7.30–7.29 (m, 1H), 5.42 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 163.7, 156.2, 141.1, 140.0, 138.9, 138.0, 135.8., 135.7, 134.1, 132.8, 131.3, 129.4, 128.9, 128.4, 127.5,

127.4, 127.3, 126.9, 126.6, 124.6, 123.3, 119.9, 116.4, 112.1, 60.1; IR ν_{max} (neat)/cm^{-1}: 3344 (w), 1725 (w), 1448 (w), 1174 (m), 722 (s); HRMS (ESI) calcd for $C_{29}H_{19}Cl_2N_2O_6S$ $[M-H]^-$: 593.0341, found 593.0329.



IS8

(7-Methyl-1-(phenylsulfonyl)-1H-indol-3-yl)methyl 2,4-dichlorobenzoyloxycarbamate(IS8): white solid, mp: 130–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.46 (brs, 1H), 8.15 (s, 4H), 7.93 (s, 1H), 7.70 (d, J = 7.6 Hz, 2H), 7.58 (t, J = 7.2 Hz, 1H), 7.49-7.45 (m, 3H), 7.16 (t, J = 7.6 Hz, 1H), 7.06 (d, J = 7.2 Hz, 1H), 5.44 (s, 2H), 3.98 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 165.9, 165.0, 156.2, 139.7, 135.1, 133.7, 131.2, 130.2, 129.9, 129.8, 129.6, 129.4, 128.8, 126.4, 124.9, 124.0, 117.3, 115.7, 60.1, 52.6, 21.6; ν_{max} (neat)/cm^{-1}: 3260 (w), 1725 (s), 1361 (m), 1227 (s), 1087 (s); HRMS (ESI) calcd for $C_{26}H_{21}N_2O_8S$ $[M-H]^-$: 521.1019, found 521.1030.



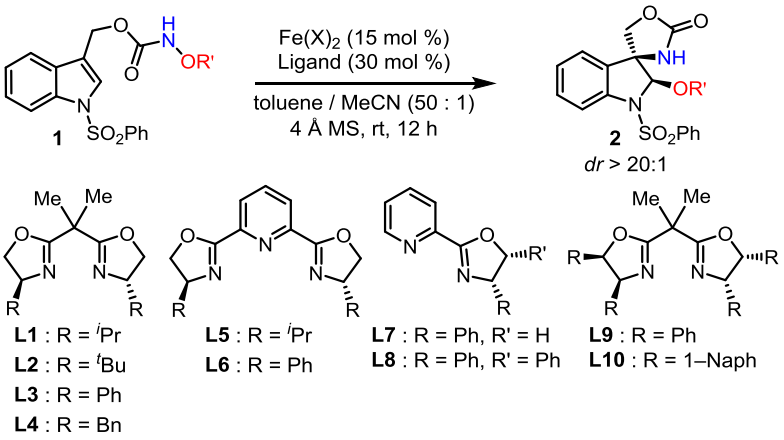
IS9

(4-Bromo-1-(phenylsulfonyl)-1H-indol-3-yl)methyl 2,4-dichlorobenzoyloxycarbamate (IS9): ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.58 (s, 1H), 7.97-7.95 (d, J = 8.4 Hz, 1H), 7.91-7.89 (m, 3H), 7.78 (s, 1H), 7.56 (t, J = 7.2 Hz, 1H), 7.49-7.44 (m, 3H), 7.39 (d, J = 7.6 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.17 (t, J = 8.0 Hz, 1H), 5.60 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 163.7, 156.0, 139.8, 137.5, 136.1, 135.7, 134.3, 132.8, 131.2, 129.4, 127.8, 127.7, 127.2, 126.9, 125.9, 124.6, 116.6, 114.1, 112.7, 60.5; IR ν_{max} (neat)/cm^{-1}:

3006 (w), 1745 (m), 1374 (m), 983 (s), 722 (s); HRMS (ESI) calcd for $C_{23}H_{14}BrCl_2N_2O_6S$ [M-H]$^-$: 594.9133, found 594.9149.

3.2.3 Catalyst Discovery for Enantioselective Intramolecular Indole Aminohydroxylation

3.2.3.1 General Procedure



entry[a]	$Fe(X)_2$	ligand	R'	yield[b]	ee[c]
1	$Fe(OTf)_2$	**L1**	2,4-Cl_2-benzoyl	22%	0%
2	$Fe(OTf)_2$	**L2**	2,4-Cl_2-benzoyl	25%	31%
3	$Fe(OTf)_2$	**L3**	2,4-Cl_2-benzoyl	58%	77%
4[d]	$Fe(OTf)_2$	**L4**	2,4-Cl_2-benzoyl	48%	-86%
5	$Fe(OTf)_2$	**L5**	2,4-Cl_2-benzoyl	15%	32%
6	$Fe(OTf)_2$	**L6**	2,4-Cl_2-benzoyl	33%	22%
7	$Fe(OTf)_2$	**L7**	2,4-Cl_2-benzoyl	21%	37%
8	$Fe(OTf)_2$	**L8**	2,4-Cl_2-benzoyl	25%	61%
9	$Fe(OTf)_2$	**L9**	2,4-Cl_2-benzoyl	65%	87%
10	$Fe(OTf)_2$	**L10**	2,4-Cl_2-benzoyl	50%	81%
11	$Fe(OTf)_2$	**L9**	4-CO_2Me-benzoyl	62%	87%
12	$Fe(OTf)_2$	**L9**	4-CF_3-benzoyl	65%	77%
13	$Fe(OTf)_2$	**L9**	4-Cl-benzoyl	58%	78%
14	$Fe(OTf)_2$	**L9**	3,5-$(CF_3)_2$-benzoyl	75%	75%
15	$Fe(NTf_2)_2$	**L9**	2,4-Cl_2-benzoyl	67%	79%
16	$FeCl_2$	**L9**	2,4-Cl_2-benzoyl	63%	86%
17	$FeBr_2$	**L9**	2,4-Cl_2-benzoyl	52%	75%
18	$Fe(OAc)_2$	**L9**	2,4-Cl_2-benzoyl	67%	90%

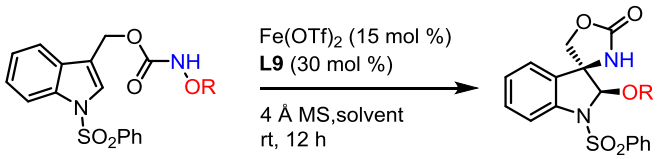
[a]Reactions were carried out under argon in 0.025 M toluene/MeCN (50:1) mixture; catalyst complexes were formed by premixing $Fe(X)_2$ and ligands for 40 min. [b]Isolated yield. [c]ee was measured by HPLC analysis with chiral stationary phase. [d]The sense of enantioinduction in entry 4 is opposite to that of other entries.

Table 11. Catalyst Discovery for Intramolecular Indole Aminohydroxylation

4 Å MS (50 mg), $Fe(X)_2$ (0.007 mmol) and chiral ligand **L** (0.014 mmol)were added to a flame-dried vial. After evacuation upon oil pump and refill with argon three times, anhydrous and degassed toluene/MeCN (50:1, 1.5 mL) mixture was added. The obtained suspension was stirred vigorously at room temperature for 30 min when the substrate (0.04 mmol) in the aforementioned co-solvent (0.5 mL) was added. The reaction mixture was stirred at room temperature for 12 h before quenched by saturated $NaHCO_3$ aqueous solution. The aqueous phase was extracted with DCM three times. The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by silica gel flash column (hexane:THF = 4:1) afforded the aminohydroxylation product **2**.

3.2.3.2 Solvent Screening

A series of toluene and MeCN co-solvent systems have been screened for the asymmetric reaction with the aforementioned procedure (Table **12**).

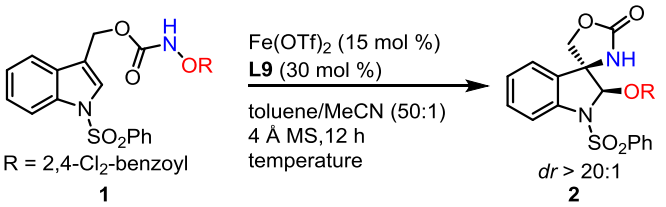


1 **2**

entry	solvent	ratio	*ee*
1	toluene	-	85%
2	toluene/MeCN	5:1	80%
3	toluene/MeCN	10:1	81%
4	toluene/MeCN	20:1	81%
5	toluene/MeCN	50:1	87%
6	MeCN	-	49%

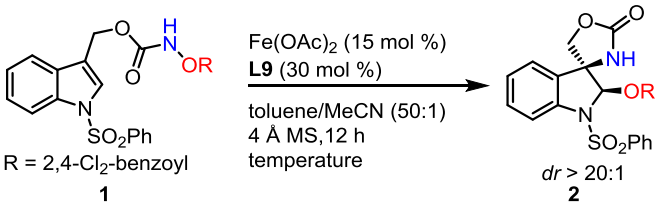
Table 12. Solvent Screening for $Fe(OTf)_2$–**L9** System

3.2.3.3 Temperature Screening



entry	temperature	conversion	*ee*
1	rt	>95%	87%
2	0 °C	65%	87%

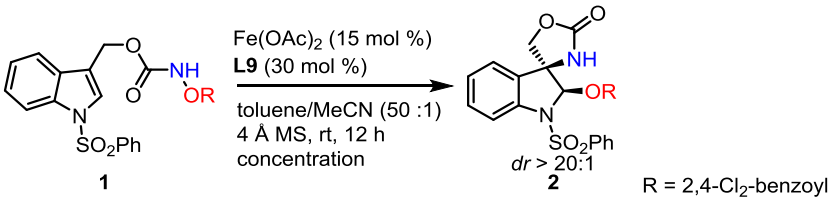
Table 13. Temperature Screening for $Fe(OTf)_2$–**L9**-Catalyzed Reactions



entry	temperature	conversion	*ee*
1	rt	>95%	90%
2	0 °C	<50%	90%

Table 14. Temperature Screening for $Fe(OAc)_2$–**L9**-Catalyzed Reactions

3.2.3.4 Concentration Screening

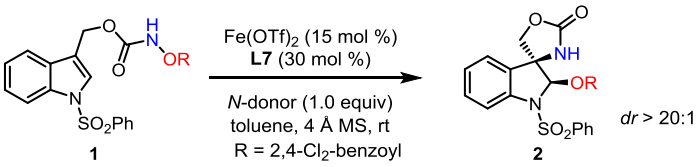


entry	concentration	*ee*
1	0.10 M	82%
2	0.05 M	87%
3	0.02 M	90%
4	0.01 M	90%

Table 15. Concentration Screening for $Fe(OAc)_2$–**L9**-Catalyzed Reactions

3.2.3.5 N-Donor Effect

General Procedure for *N*–donor Additive's Effect: To a flame-dried vial were added 4 Å MS (50 mg), $Fe(OTf)_2$ (0.007 mmol) and ligand **L9** (0.014 mmol). After evacuation upon oil pump and refill with argon three times, the anhydrous and degassed toluene was added, followed by addition of the *N*–donor compound (0.04 mmol). The obtained suspension was stirred vigorously at room temperature for 30 min when the substrate (0.04 mmol) dissolved anhydrous and degassed toluene (600 μL) was added in one portion. The reaction was stirred at room temperature for indicated time above and quenched by saturated $NaHCO_3$ aqueous solution. The aqueous phase was extracted with DCM three times. The combined organic phase was dried over anhydrous Na_2SO_4. After concentration *in vacuo*, the residue was purified by silica gel flash column chromatography (hexane:THF = 4:1).



1 2

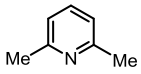
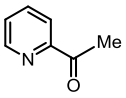
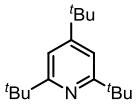
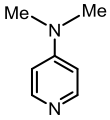
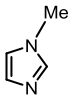
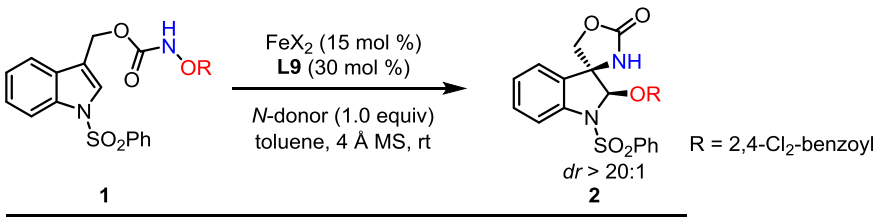
entry	*N*-donor	time for full conversion	*ee*
1		0.5 h	85%
2		1.0 h	80%
3		12 h	79%
4		12 h	87%
5		non-reactive	NA
6		non-reactive	NA

Table 16. *N*-Donor Additive Effect

In the presence of lutidine as the *N*–donor additive, a series of iron (II) salts with different counter anions were screened (Table **17**).

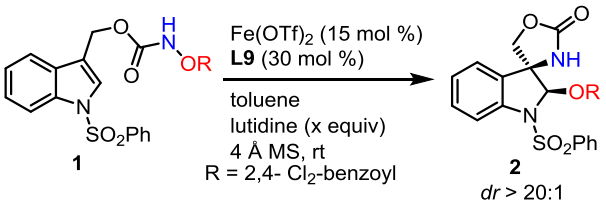


1 **2**

entry	FeX_2	time for full conversion	*ee*
1	$Fe(OTf)_2$	0.5 h	85%
2	$Fe(OAc)_2$	12 h	89%
3	$Fe(NTf_2)_2$	12 h	79%

Table 17. Counter Anion Screening with Lutidine as the *N*-donor

Experiments with different quantities of lutidine were performed for *ee* optimization (Table **18**).

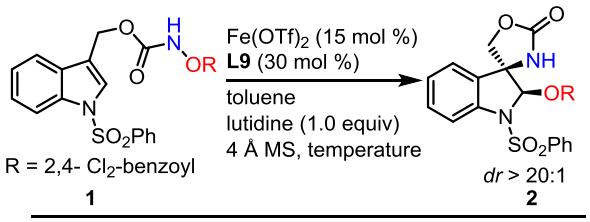


1 **2**

entry	x	time for full conversion	*ee*
1	0.2	0.5 h	82%
2	1.0	0.5 h	85%
3	5.0	0.5 h	82%
4	10.0	0.5 h	76%

Table 18. Lutidine Quantity Screening

The temperature screening showed that the highest enantioselectivity is obtained at -10 °C (Table **19**).



1 **2**

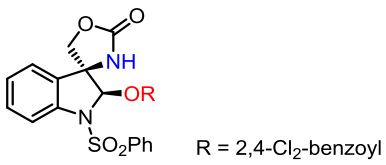
entry	temperature	time	*ee*
1	rt	0.5 h	85%
2	-10 °C	0.5 h	88%
3	-30 °C	0.5 h	84%

Table 19. Temperature Screening for the Additive Effect

3.2.3.6 General Procedure for Iron(II)-Catalyzed Asymmetric Aminohydroxylation

To a flame-dried vial were added 4Å MS (50 mg), $Fe(OAc)_2$ (0.007 mmol) together with ligand **L9** (0.014 mmol). After evacuation upon oil pump and refill with argon three times, anhydrous and degassed toluene/MeCN (50:1, 1.5 mL) co-solvent was added. The obtained suspension was stirred vigorously at room temperature for 30 min before the substrate (0.04 mmol) in the aforementioned co-solvent (0.5 mL) was added in one portion. The reaction system was stirred at room temperature for 12 h when all the starting material was fully consumed. Sat. $NaHCO_3$ aqueous solution was added to quench the reaction, and the aqueous phase was extracted with DCM three times. The combined organic phase was dried over anhydrous Na2SO4 and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (hexane:THF = 4:1) to give the desired aminohydroxylation product **2**.

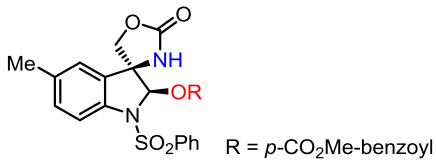
3.2.3.7 Product Characterization



2

(2*R*, 3*S*)-2'-Oxo-1-(phenylsulfonyl)spiro[indoline-3,4'-oxazolidine]-2-yl 2,4-

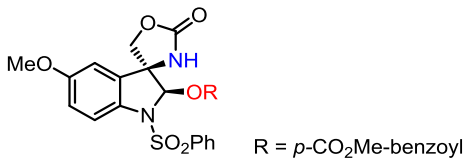
dichlorobenzoate (2): by following the general procedure (0.04 mmol scale), the title compound **2** was obtained from **1** and isolated by a silica gel flash column as white foam (14 mg, 67% yield). The sample was analyzed by Chiral HPLC analysis and determined to be 90% *ee* (Chiralcel AD-H, 1.0 mL/min, 272 nm, 20% *i*-PrOH in hexane, t_r (minor) = 19.99 min, t_r (major) = 32.33 min). $[\alpha]_D^{20}$ = 62.0° (c = 1.0, DCM). ^{1}H NMR (400 MHz, d_6-DMSO, ppm): δ 8.80 (s, 1H), 8.02 (d, J = 7.6 Hz, 2H), 7.84 (s, 1H), 7.77 (d, J = 8.4 Hz, 1H)， 7.69 (t, J = 6.8 Hz, 1H), 7.57-7.54 (m, 3H), 7.49 (d, J = 6.8 Hz, 1H), 7.41 (s, 2H), 7.21 (s, 1H), 6.99 (s, 1H), 4.62 (d, J = 9.2 Hz, 1H), 4.06 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, d_6-DMSO, ppm): δ 162.7, 158.1, 150.4, 139.5, 138.7, 138.0, 134.9, 134.8, 133.7, 131.4, 131.2, 130.2, 129.7, 128.0, 127.7, 127.0, 125.7, 125.4, 113.5, 89.4, 73.9, 67.0; HRMS (ESI) calcd for $C_{23}H_{15}Cl_2N_2O_6S$ $[M-H]^-$: 517.0028, found 517.0042.



P2

Methyl (2*R*,3*S*)-5-ethyl-2'-oxo-1-(phenylsulfonyl)spiro[indoline-3,4'-oxazolidine]-2-yl terephthalate (P2): by following the general procedure (0.04 mmol scale), the title compound **P2** was obtained from **IS2** and isolated by a silica gel flash column as white foam (16 mg, 72% yield). The sample was analyzed by Chiral HPLC analysis and determined to be 94% *ee* (Chiralcel AD-H, 1.0 mL/min, 254 nm, 20% *i*-PrOH in hexane, t_r (minor) = 18.86 min, t_r (major) = 24.41 min). $[\alpha]_D^{20}$ = 32.0° (c = 1.1, DCM). ^{1}H NMR (400 MHz, d_6-DMSO, ppm): δ 8.80 (s, 1H), 8.08 (d, J = 8.0 Hz, 2H), 7.97 (d, J = 7.6 Hz, 4H), 7.69 (t, J = 7.2 Hz, 1H), 7.55 (t, J = 7.6 Hz, 2H), 7.35 (d, J = 8.0 Hz, 1H), 7.29 (s, 1H), 7.25 (d, J = 8.0 Hz, 1H), 6.97 (s, 1H), 4.52 (d, J = 9.2 Hz, 1H), 4.01 (d, J = 9.2 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO, ppm): δ

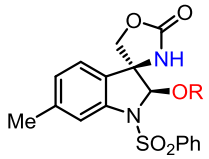
165.9, 164.3, 158.2, 138.1, 137.3, 135.1, 134.9, 134.6, 132.5, 131.8, 130.7, 130.3, 129.9, 129.8, 127.5, 125.8, 113.6, 89.5, 73.8, 67.1, 53.1, 20.9; IR ν_{max} (neat)/cm^{-1}: 3324 (w), 1767 (s), 1276 (m), 1176 (m); HRMS (ESI) calcd for $C_{24}H_{18}Cl_2N_2O_6S$ [M-H]$^-$: 531.0184, found 531.0192.



P3

(2*R*,3*S*)-5-methoxy-2'-oxo-1-(phenylsulfonyl)spiro[indoline-3,4'-oxazolidine]-2-yl methyl terephthalate (P3): the title compound **P3** was obtained from **IS3** by following the general procedure with lutidine as the additive. To a flame-dried vial were added 4 Å MS (50 mg), $Fe(OTf)_2$ (0.007 mmol) and ligand **L9** (0.014 mmol). After evacuation upon oil pump and refill with argon three times, anhydrous and degassed toluene (1.4 mL) was added, followed by addition of lutidine (0.04 mmol). The obtained suspension was stirred vigorously at room temperature for 30 min and then **IS3** (0.04 mmol) dissolved anhydrous and degassed toluene (600 μL) was added in one portion. The reaction was stirred at room temperature for 1 h and quenched by saturated $NaHCO_3$ aqueous solution. The aqueous phase was extracted with DCM three times and the combined organic phase was dried over anhydrous Na_2SO_4. After concentration *in vacuo*, the title compound was isolated by a silica gel flash column as white foam (17 mg, 75% yield). The sample was analyzed by Chiral HPLC analysis and determined to be 93% *ee* (Chiralcel AD-H, 1.0 mL/min, 272 nm, 20% *i*-PrOH in hexane, t_r (minor) = 20.03 min, t_r (major) = 21.67 min). $[\alpha]_D^{20}$ = 30.5^o (c = 1.3, DCM). ^{1}H NMR (400 MHz, d_6-DMSO, ppm): δ 8.81 (s, 1H), 8.03 (AB, 4H), 7.94 (d, *J* = 7.6 Hz, 2H), 7.70 (t, *J* = 7.2 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.8 Hz, 1H), 7.09 (d, *J* = 2.0 Hz, 1H), 7.01 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 6.93 (s, 1H), 4.36 (d, *J* = 9.2 Hz, 1H), 4.03 (d, *J* = 8.8 Hz, 1H), 3.90 (s, 3H), 3.75 (s, 3H);

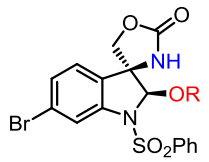
^{13}C NMR (100 MHz, d_6-DMSO, ppm): δ 165.9, 164.3, 158.1, 157.6, 137.9, 134.9, 134.6, 132.8, 132.5, 131.4, 130.7, 130.3, 129.8, 127.5, 117.0, 115.1, 110.9, 89.7, 73.5, 67.3, 56.2, 53.1; IR ν_{max} (neat)/cm^{-1}: 3330 (w), 1771 (s), 1275 (m), 1033 (s); MS(ESI) $C_{26}H_{22}N_2O_9S$ [M-H]$^-$: 537.1.



R = 2,4-Cl_2-benzoyl

P4

(2*R*, 3*S*)-6-methyl-2'-oxo-1-(phenylsulfonyl)spiro[indoline-3,4'-oxazolidine]-2-yl 2,4-dichlorobenzoate(P4): by following the general procedure (0.04 mmol scale), the title compound **P4** was obtained from **IS4** and isolated by a silica gel flash column as white foam (14 mg, 65% yield). The sample was analyzed by Chiral HPLC analysis and determined to be 94% *ee* (Chiralcel AD-H, 1.0 mL/min, 254 nm, 20% *i*-PrOH in hexane, t_r (minor) = 17.02 min, t_r (major) = 28.59 min). $[\alpha]_D^{20}$ = 25.9^o (c = 1.1, DCM). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.75 (s, 1H), 8.01 (d, *J* = 7.6 Hz, 2H), 7.84 (s, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.68 (d, *J* = 7.2 Hz, 1H), 7.57–7.55 (m, 3H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.24 (s, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.94 (s, 1H), 4.53 (d, *J* = 9.2 Hz, 1H), 4.01 (d, *J* = 9.2 Hz, 1H), 3.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 162.2, 157.6, 141.1, 139.3, 138.2, 137.6, 134.4, 134.3, 133.2, 130.7, 129.8, 127.5, 127.2, 126.5, 126.4, 125.7, 124.8, 13.6, 89.2, 73.4, 66.4, 21.3; IR ν_{max} (neat)/cm^{-1}: 3342 (w), 1634 (w), 1276 (m), 750 (s); HRMS (ESI) calcd for $C_{24}H_{18}Cl_2N_2O_6S$ [M-H]$^-$: 531.0184, found 531.0193.

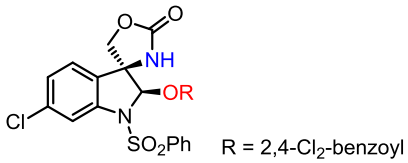


R = 2,4-Cl_2-benzoyl

P5

(2*R*, 3*S*)-6-bromo-2'-oxo-1-(phenylsulfonyl)spiro[indoline-3,4'-oxazolidine]-2-yl 2,4-dichlorobenzoate (P5): by following the general procedure (0.04 mmol scale), the title

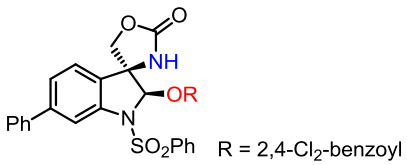
compound **P5** was obtained from **IS5** and isolated by a silica gel flash column as white foam (16 mg, 64% yield). The sample was analyzed by Chiral HPLC analysis and determined to be 98% *ee* (Chiralcel AD-H, 1.0 mL/min, 272 nm, 20% *i*-PrOH in hexane, t_r (minor) = 20.19 min, t_r (major) = 28.35 min). $[\alpha]_D^{20}$ = 13.1° (c = 0.87, DCM). ^{1}H NMR (400 MHz, d_6-DMSO, ppm): δ 8.83 (s, 1H), 8.04 (d, J = 7.6 Hz, 2H), 7.83 (d, J = 1.6 Hz, 1H), 7.77–7.71 (m, 2H), 7.61–7.55 (m, 3H), 7.49–7.43 (m, 3H), 7.00 (s, 1H), 4.64 (d, J = 9.2 Hz, 1H), 4.10 (d, J = 9.2 Hz, 1H);^{13}C NMR (100 MHz, d_6-DMSO, ppm): δ 162.0, 157.5, 140.5, 138.3, 137.4, 134.8, 134.4, 133.3, 130.8, 130.0, 128.9, 127.8, 127.6, 127.2, 126.3, 123.5, 115.5, 89.0, 73.1, 66.2; IR ν_{max} (neat)/cm^{-1}: 3290 (m), 1647 (w), 1276 (w), 1016 (s), 750 (s); HRMS (ESI) calcd for $C_{23}H_{14}BrCl_2N_2O_6S$ $[M-H]^-$: 594.9133, found 594.9147.



P6

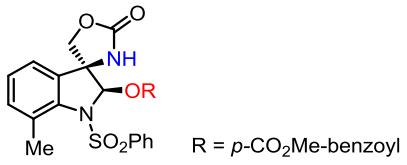
(2*R*, 3*S*)-6-chloro-2'-oxo-1-(phenylsulfonyl)spiro[indoline-3,4'-oxazolidine]-2-yl 2,4-dichlorobenzoate (P6): by following the general procedure (0.04 mmol scale), the title compound **P6** was obtained from **IS6** and isolated by a silica gel flash column as white foam (16 mg, 70% yield). The sample was analyzed by Chiral HPLC analysis and determined to be 99% *ee* (Chiralcel AD-H, 1.0 mL/min, 272 nm, 20% *i*-PrOH in hexane, t_r (minor) = 18.39 min, t_r (major) = 26.10 min). $[\alpha]_D^{20}$ = 10.1° (c = 0.67, DCM). ^{1}H NMR (400 MHz, d_6-DMSO, ppm): δ 8.82 (s, 1H), 8.05 (d, J = 7.6 Hz, 2H), 7.83 (d, J = 1.6 Hz, 1H), 7.76–7.70 (m, 2H), 7.61–7.54 (m, 4H), 7.35 (s, 1H), 7.29 (d, J = 7.6 Hz, 1H), 7.01 (s, 1H), 4.65 (d, J = 9.2 Hz, 1H), 4.10 (d, J = 9.2 Hz, 1H);^{13}C NMR (100 MHz, d_6-DMSO, ppm): δ 162.0, 157.5, 140.4, 138.3, 137.4, 135.2, 134.7, 134.4, 133.2, 130.8, 130.0, 128.4, 127.5, 127.2, 126.9, 126.3, 124.9, 112.8, 89.1, 73.1,

66.2; IR ν_{max} (neat)/cm^{-1}: 3260 (w), 1767 (s), 1586 (m), 1376 (m), 1027 (s); HRMS (ESI) calcd for $C_{23}H_{14}Cl_3N_2O_6S$ $[M-H]^-$: 550.9638, found 550.9640.



P7

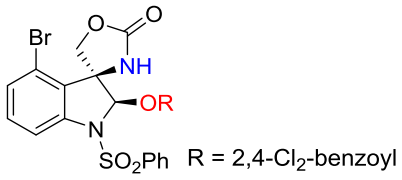
(2*R*, 3*S*)-2'-oxo-6-phenyl-1-(phenylsulfonyl)spiro[indoline-3,4'-oxazolidine]-2-yl 2,4-dichlorobenzoate (P7): by following the procedure for preparation of **P3** (0.04 mmol scale), the title compound **P7** was obtained from **IS7** and isolated by a silica gel flash column as white foam (16 mg, 65% yield).The sample was analyzed by Chiral HPLC analysis and determined to be 91% *ee* (Chiralcel AD-H, 1.0 mL/min, 272 nm, 20% *i*-PrOH in hexane, t_r (minor) = 20.43 min, t_r (major) = 27.22 min). $[\alpha]_D^{20}$ = 17.5^o (c = 0.6, DCM). ^{1}H NMR (400 MHz, d_6-DMSO, ppm): δ 8.83 (brs, 1H), 8.06 (d, J = 7.6 Hz, 2H), 7.84 (s, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.71 (t, J = 7.2 Hz, 1H), 7.62–7.44 (m, 11H), 7.03 (s, 1H), 4.62 (d, J = 9.2 Hz, 1H), 4.12 (d, J = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, d_6-DMSO, ppm): δ 162.6, 158.1, 143.7, 140.4, 139.8, 138.7, 138.0, 135.1, 134.8, 133.7, 131.2, 130.4, 129.7, 128.9, 128.7, 128.0, 127.7, 127.4, 127.0, 126.2, 124.3, 111.5, 89.7, 73.8, 66.8; IR ν_{max} (neat)/cm^{-1}: 3354 (w), 1765 (s), 1376 (m), 1172 (m), 763 (m); HRMS (ESI) calcd for $C_{29}H_{20}Cl_2N_2O_6SNa$ $[M+Na]^+$: 617.0317, found 617.0311.



P8

Methyl (*2R*, 3*S*)-7-methyl-2'-oxo-1-(phenylsulfonyl)spiro[indoline-3,4'-oxazolidine]-2-yl terephthalate (P8): by following the general procedure (0.04 mmol scale), the title compound **P8** was obtained from **IS8** and isolated by a silica gel flash column as white foam (13

mg, 62% yield). The sample was analyzed by Chiral HPLC analysis and determined to be 88% *ee* (Chiralcel AD-H, 1.0 mL/min, 254 nm, 20% EtOH in hexane, t_r (minor) = 20.81 min, t_r (major) = 23.31 min). $[\alpha]_D^{20}$ = -19.1^o (*c* = 0.8, DCM). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.07 (d, *J* = 8.0 Hz, 2H), 7.96 (d, *J* = 7.6 Hz, 2H), 7.92 (d, *J* = 8.0 Hz, 2H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 7.2 Hz, 2H), 7.28 (s, 2H), 7.20 (d, *J* = 3.6 Hz, 1H), 7.05 (s, 1H), 5.95 (s, 1H), 4.46 (d, *J* = 9.6 Hz, 1H), 4.03 (d, *J* = 9.2 Hz, 1H), 3.94 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 165.9, 139.0, 134.9, 133.9, 133.8, 131.8, 131.0, 130.0, 129.7, 129.3, 127.8, 127.5, 121.0, 89.7, 73.9, 68.0, 52.6, 20.2; IR ν_{max} (neat)/cm^{-1}: 2922 (w), 1727 (s), 1279 (s), 1116 (m); HRMS (ESI) calcd for $C_{26}H_{22}N_2O_8S$ $[M-H]^-$: 521.1019, found 521.1014.

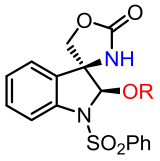


P9

(2R, 3S)-4-bromo-2'-oxo-1-(phenylsulfonyl)spiro[indoline-3,4'-oxazolidine]-2-yl 2,4-dichlorobenzoate (P9): by following the general procedure (0.04 mmol scale), the title compound **P9** was obtained from **IS9** and isolated by a silica gel flash column as white foam (16 mg, 67% yield). The sample was analyzed by Chiral HPLC analysis and determined to be 74% *ee* (Chiralcel AD-H, 1.0 mL/min, 254 nm, 20% *i*-PrOH in hexane, t_r (minor) = 13.59 min, t_r (major) = 27.94 min). $[\alpha]_D^{20}$ = 14.3^o (*c* = 0.35, DCM). ^{1}H NMR (400 MHz, d_6-DMSO, ppm): δ 8.81 (s, 1H), 8.04 (d, *J* = 7.6 Hz, 2H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.85 (s, 1H), 7.72 (t, *J* = 7.2 Hz, 1H), 7.60-7.55 (m, 3H), 7.43-7.33 (m, 3H), 7.04 (s, 1H), 4.83 (d, *J* = 9.2 Hz, 1H), 7.24 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 162.2, 157.5, 141.4, 138.3, 137.4, 134.6, 134.3, 133.2, 132.7, 130.7, 129.8, 128.9, 127.5, 127.3, 126.5, 126.48, 119.6, 112.4, 89.9, 71.4, 67.1; IR ν_{max} (neat)/cm^{-1}: 3241 (w), 1759 (m), 1582 (m), 1026 (s), 728 (s); HRMS (ESI) calcd for

$C_{23}H_{14}BrCl_2N_2O_6S$ [M-H]$^-$: 594.9133, found 594.9140.

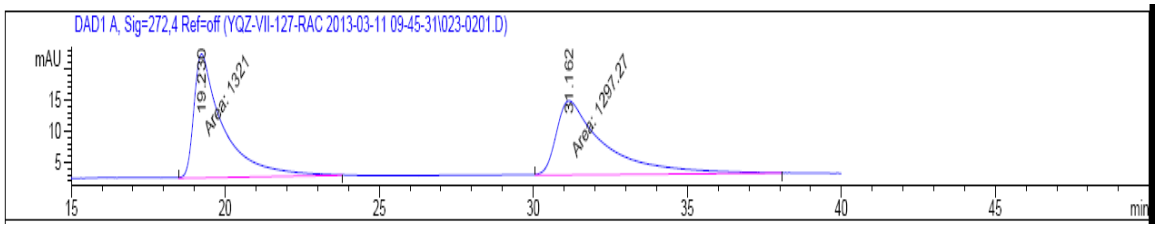
3.2.3.8 HPLC Data



R = 2,4-Cl_2-benzoyl

2

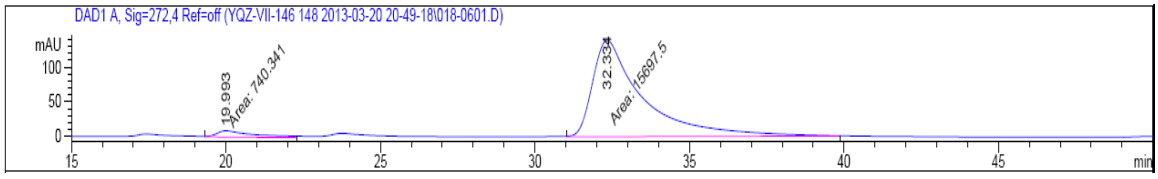
Racemic sample:



Signal 1: DAD1 A, Sig=272,4 Ref=off

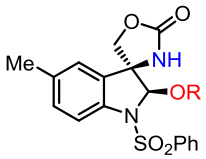
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.230	MM	1.1054	1321.00183	19.91783	50.4531
2	31.162	MM	1.8157	1297.27380	11.90822	49.5469

90% *ee*



Signal 1: DAD1 A, Sig=272,4 Ref=off

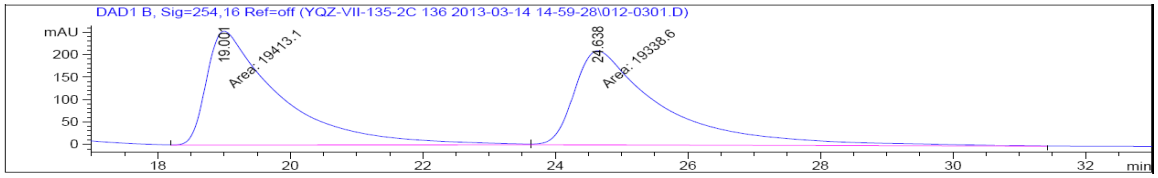
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.993	MM	1.3822	740.34070	8.92688	4.5039
2	32.334	MM	1.8809	1.56975e4	139.09419	95.4961



R = *p*-CO_2Me-benzoyl

P2

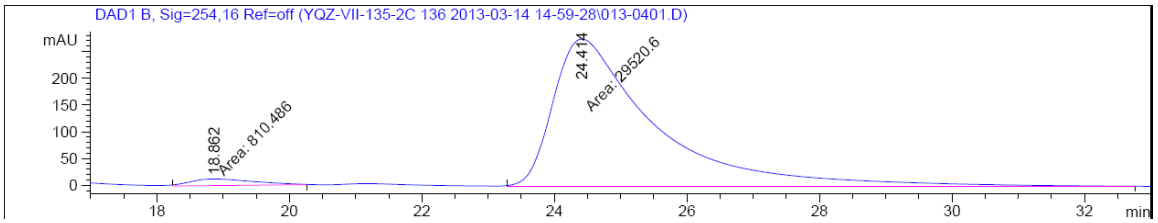
Racemic sample:



Signal 2: DAD1 B, Sig=254,16 Ref=off

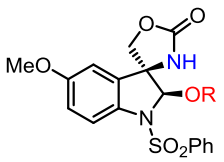
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.001	MM	1.2738	1.94131e4	253.99942	50.0961
2	24.638	MM	1.5357	1.93386e4	209.88080	49.9039

94% *ee*



Signal 2: DAD1 B, Sig=254,16 Ref=off

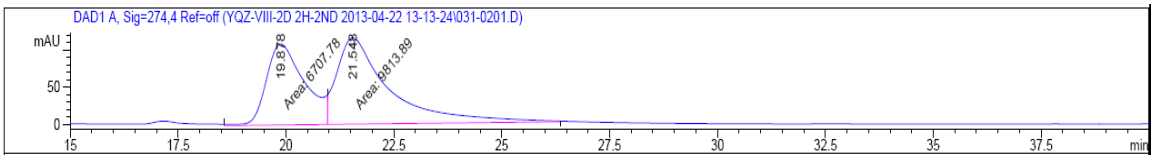
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.862	MM	1.1015	810.48639	12.26366	2.6721
2	24.414	MM	1.7846	2.95206e4	275.70087	97.3279



R = *p*-CO_2Me-benzoyl

P3

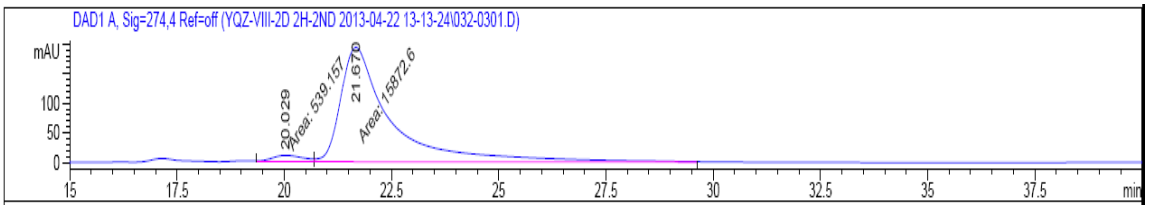
Racemic sample:



Signal 1: DAD1 A, Sig=274,4 Ref=off

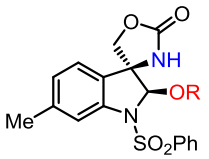
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.878	MF	1.0266	6707.78027	108.90113	40.5999
2	21.548	FM	1.4083	9813.88770	116.14644	59.4001

93% *ee*



Signal 1: DAD1 A, Sig=274,4 Ref=off

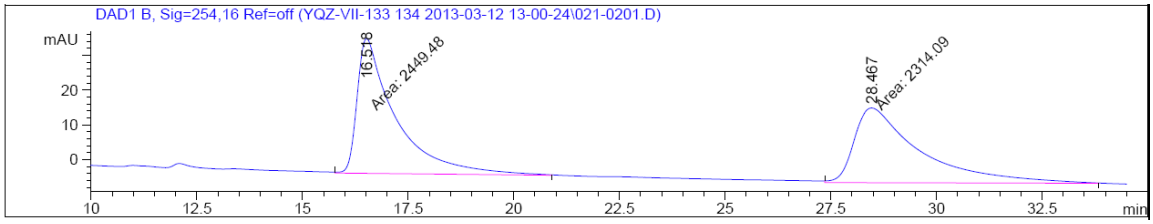
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.029	MF	0.8448	539.15747	10.63658	3.2852
2	21.670	FM	1.3706	1.58726e4	193.00690	96.7148



R = 2,4-Cl_2-benzoyl

P4

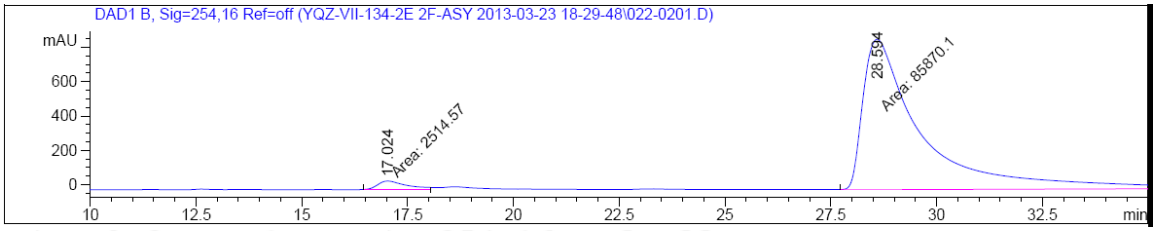
Racemic sample:



Signal 2: DAD1 B, Sig=254,16 Ref=off

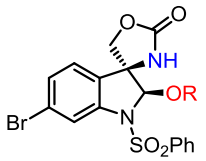
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.518	MM	1.0530	2449.47583	38.76852	51.4211
2	28.467	MM	1.7952	2314.08838	21.48346	48.5789

94% *ee*



Signal 2: DAD1 B, Sig=254,16 Ref=off

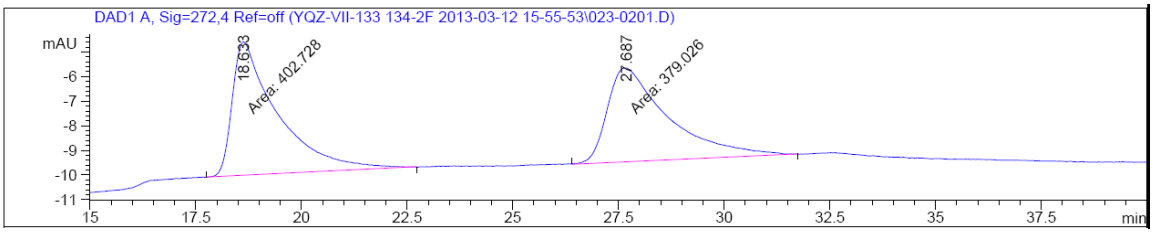
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.024	MM	0.8195	2514.57104	51.14065	2.8450
2	28.594	MM	1.6314	8.58701e4	877.24841	97.1550



R = 2,4-Cl_2-benzoyl

P5

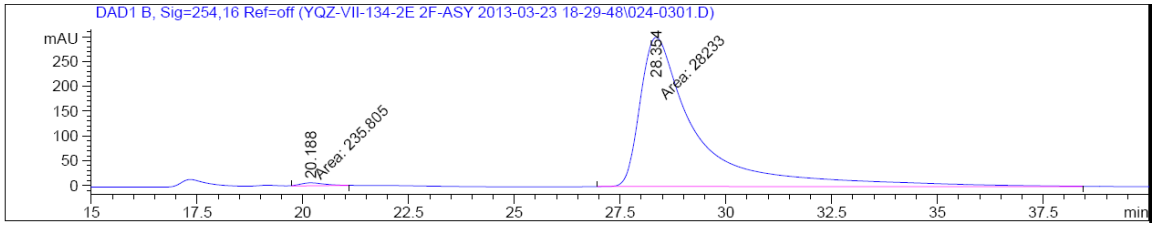
Racemic sample:



Signal 1: DAD1 A, Sig=272,4 Ref=off

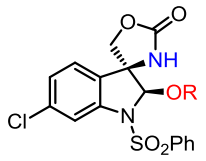
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.633	MM	1.2394	402.72781	5.41551	51.5159
2	27.687	MM	1.6570	379.02621	3.81235	48.4841

98% *ee*



Signal 2: DAD1 B, Sig=254,16 Ref=off

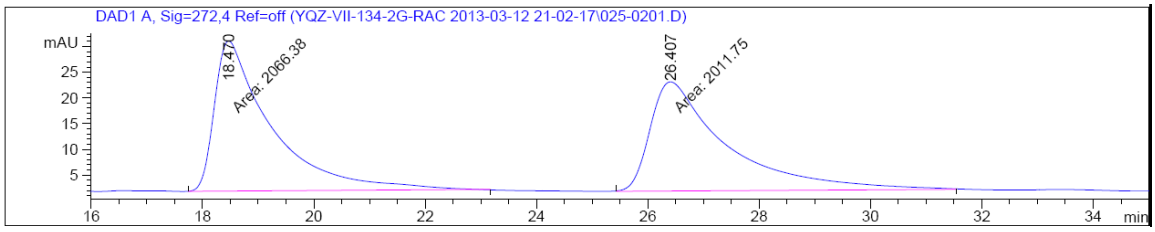
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.188	MM	0.6578	235.80507	5.97425	0.8283
2	28.354	MM	1.5651	2.82330e4	300.64658	99.1717



R = 2,4-Cl_2-benzoyl

P6

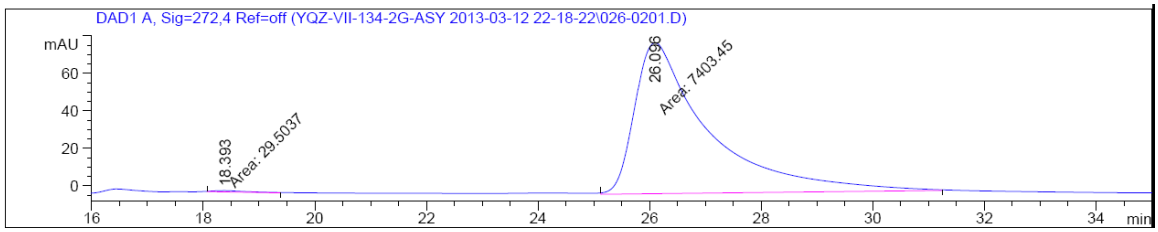
Racemic sample:



Signal 1: DAD1 A, Sig=272,4 Ref=off

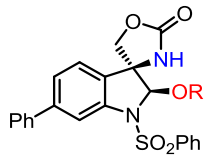
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.470	MM	1.1800	2066.38477	29.18551	50.6699
2	26.407	MM	1.5799	2011.74622	21.22199	49.3301

99% *ee*



Signal 1: DAD1 A, Sig=272,4 Ref=off

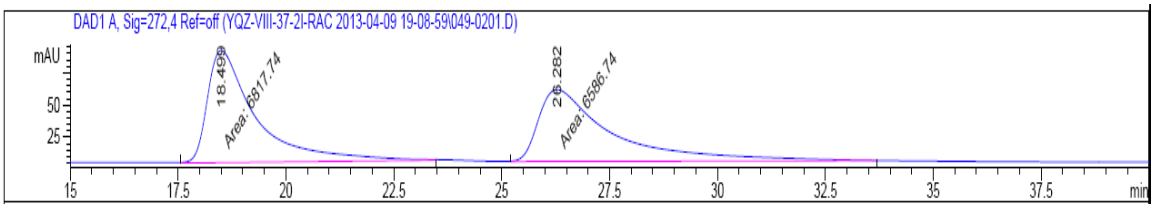
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.393	MM	0.7384	29.50368	6.65903e-1	0.3969
2	26.096	MM	1.5331	7403.45215	80.48215	99.6031



R = 2,4-Cl_2-benzoyl

P7

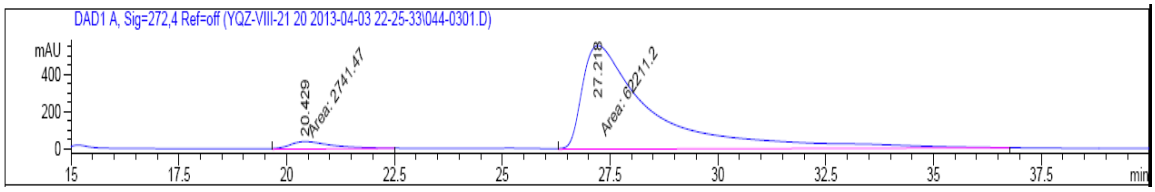
Racemic sample:



Signal 1: DAD1 A, Sig=272,4 Ref=off

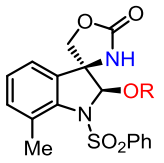
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.499	MM	1.3049	6817.73682	87.07579	50.8616
2	26.282	MM	1.9619	6586.74170	55.95666	49.1384

91% *ee*



Signal 1: DAD1 A, Sig=272,4 Ref=off

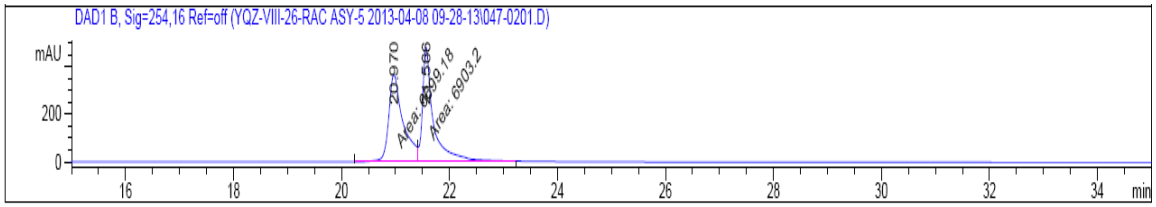
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.429	MM	1.1509	2741.47095	39.69990	4.2207
2	27.218	MM	1.8750	6.22112e4	552.98376	95.7793



R = 4-CO_2Me-benzoyl

P8

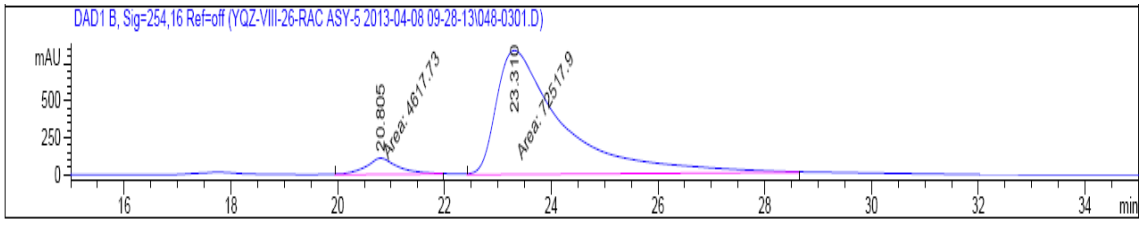
Racemic sample:



Signal 2: DAD1 B, Sig=254,16 Ref=off

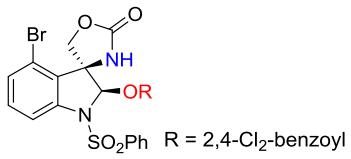
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.970	MF	0.3043	6699.18408	366.86557	49.2501
2	21.566	FM	0.2387	6903.19629	481.90265	50.7499

88% *ee*



Signal 2: DAD1 B, Sig=254,16 Ref=off

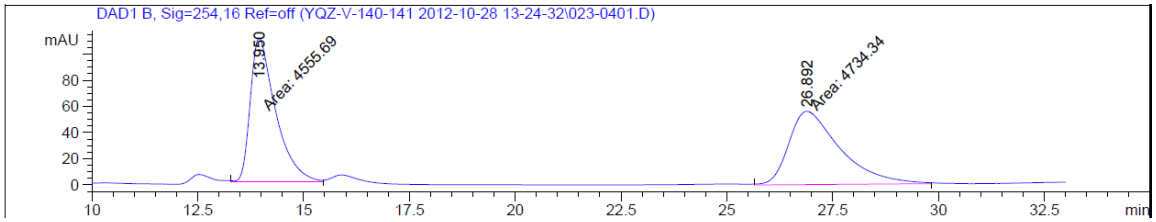
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.805	MM	0.6986	4617.72656	110.16177	5.9865
2	23.310	MM	1.4453	7.25179e4	836.27386	94.0135



R = 2,4-Cl_2-benzoyl

P9

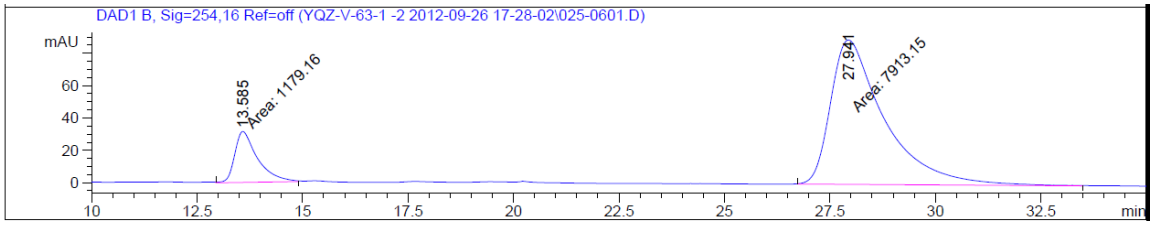
Racemic sample:



Signal 2: DAD1 B, Sig=254,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.950	MM	0.6920	4555.69385	109.72266	49.0385
2	26.892	MM	1.4070	4734.34277	56.08091	50.9615

74% *ee*

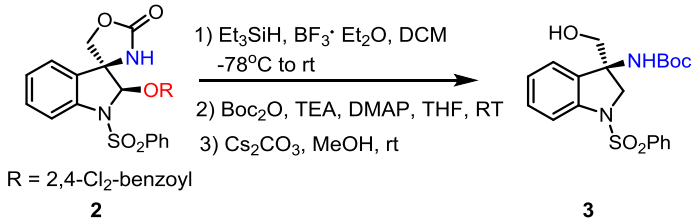


Signal 2: DAD1 B, Sig=254,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.585	MM	0.6247	1179.16479	31.45780	12.9688
2	27.941	MM	1.4784	7913.15137	89.20632	87.0312

3.2.4 Product Derivatization and its Synthetic Applications

3.2.4.1 Amino Indolane and Amino Oxindole Synthesis

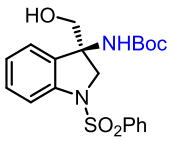


Scheme 51. Synthesis of Amino Indolane

Procedure for Amino Indolane (3) Synthesis: 2 (0.04 mmol, 21 mg) was dissolved in 2mL DCM, to which Et_3SiH (0.4 mmol, 63.0 μL) was then added, followed by addition of $BF_3{\cdot}Et_2O$ (0.12 mmol, 15μL) at -78 ℃. The mixture was stirred overnight and allowed to warm to room temperature. Then DCM was added and the organic phase was washed with water. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed under vacuum and the residue was used in the next step directly without further purification**.**

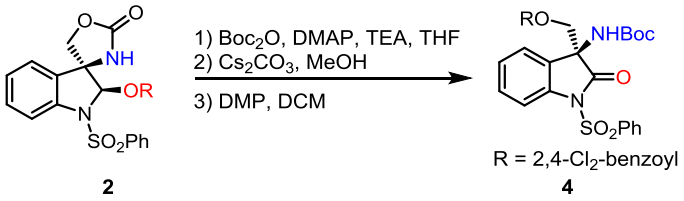
At room temperature, to a solution of the crude product obtained from the previous step in THF (2.0 mL), TEA (0.15 mmol, 21.0 μL) and DMAP (0.01 mmol, 1.2 mg) were added, followed by addition of Boc_2O (0.2 mmol, 13 mg). After stirring for 1.0h at rt, the reaction was quenched with water and extracted with DCM three times. The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The protected indolane product was dissolved in MeOH (2.0 mL), to which Cs_2CO_3 (0.04 mmol, 13 mg) was added. The reaction mixture was stirred at room temperature for 1.0 h and quenched by water. DCM was added and the organic phase was washed with water. The combined organic layers were dried over anhydrous Na_2SO_4. After filtration and concentration under vacuum, the residue was purified by silica gel flash column chromatography (hexane/EtOAc = 2:1) to afford the 3-amino indolane

(11 mg, 64% overall yield).



3

(*R*)-*tert*-Butyl (3-(hydroxymethyl)-1-(phenylsulfonyl)indolin-3-yl) carbamate(3): The sample was analyzed by Chiral HPLC analysis and determined to be 90% *ee* (Chiralcel AD-H, 1.0 mL/min, 254 nm, 10% *i*-PrOH in hexane, t_r (minor) = 25.91 min, t_r (major) = 19.08 min). $[\alpha]_D^{20}$= 4.4° (c = 1.4, DCM). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.84 (d, *J* = 7.6 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 7.2 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 7.2 Hz, 1H), 7.04 (t, *J* = 7.2 Hz, 1H), 4.14 (AB, 2H), 3.73-3.68 (m, 1H), 3,48 (s, 1H), 1.32 (s, 9H);^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 155.2, 141.7, 137.4, 133.3, 132.5, 130.0, 129.1, 127.2, 124.0, 123.5, 115.0, 80.8, 67.2, 63.24, 63.15, 57.7; IR ν_{max} (neat)/cm^{-1}: 3428 (w), 1697 (m), 1358 (m), 1168 (s); MS(ESI) calcd for $C_{20}H_{25}N_2O_5S$ $[M+H]^+$: 405.1, found: 405.2.



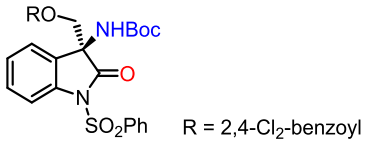
2 **4**

Scheme 52. Synthesis of Amino Oxindoles

Procedure for Synthesis of Amino Oxindoles (4): At room temperature, Boc_2O (0.11 mmol, 24 mg) was added to a solution of **2** (0.1 mmol), TEA (0.15 mmol, 20.9 μL) and DMAP (0.01 mmol, 1.2 mg) in THF (4 mL). After stirring for 1.0h, the reaction was quenched with water and extracted with DCM three times. The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Quick purification of the residue by a short flash chromatography (hexane/EtOAc) affords the crude *N*-Boc protected intermediate.

The obtained *N*-Boc protected intermediate was dissolved in 2mL MeOH, to which 2 *N* aqueous Cs_2CO_3 solution (0.02 mmol, 10 μL) was added. The mixture was stirred at room temperature for 1 h before the solvent was removed *in vacuo*. The residue was dissolved in DCM and washed with water for three times. The combined organic layers were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed to afford the crude product, which was directly subjected to next step without further purification.

To a solution of the crude product obtained above in DCM, DMP (0.12 mmol, 51 mg) was added and the mixture was stirred for 1.0 h at room temperature before water was added. The resulting mixture was extracted with DCM three times, and the combined organic layers were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by silica gel flash column chromatography (hexane/EtOAc) to afford the 3-amino oxindole product **4** (36 mg, 61% overall yield).

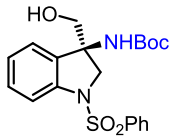


4

(*S*)-(3-((*tert*-butoxycarbonyl)amino)-2-oxo-1-(phenylsulfonyl)indolin-3-yl)methyl 2,4-dichlorobenzoate (4) : The sample was analyzed by Chiral HPLC analysis and determined to be 90% *ee* (Chiralcel AD-H, 1.0 mL/min, 254 nm, 20% *i*-PrOH in hexane, t_r (minor) = 18.18 min, t_r (major) = 31.45 min). $[\alpha]_D^{20}$ = -23.5^o (c = 1.2, DCM). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.16 (d, *J* = 7.6 Hz, 2H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.79 (s, 1H), 7.67 (t, *J* = 7.2 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 2H), 7.43–7.37 (m, 3H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.25–7.18 (m, 2H), 4.39 (AB, 2H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 171.0, 163.9, 153.2, 139.2, 137.7, 137.5, 134.4, 132.0, 131.8, 130.5, 130.2, 130.1, 128.9, 128.2, 127.5, 126.1, 125.1, 123.9, 113.7, 84.0, 67.5,

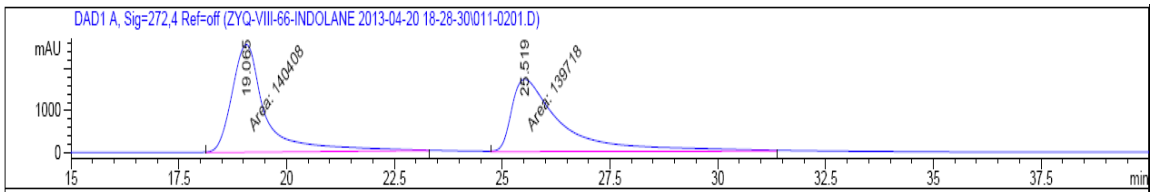
62.2, 27.6; IR ν_{max} (neat)/cm^{-1}: 3009 (w), 1754 (s), 1681 (w), 1370 (m), 1253 (s); MS (ESI) calculated for $C_{27}H_{25}Cl_2N_2O_7S$ $[M + H]^+$: 591.1, found: 591.1.

3.2.4.2 HPLC Data



3

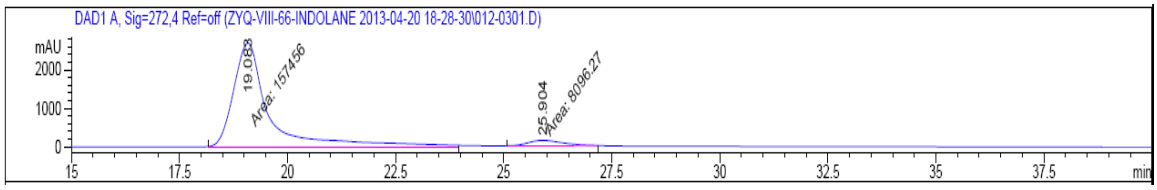
Racemic sample:



Signal 1: DAD1 A, Sig=272,4 Ref=off

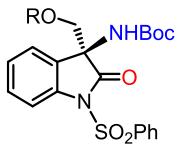
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.065	MM	0.9097	1.40408e5	2572.40405	50.1232
2	25.519	MM	1.3471	1.39718e5	1728.59094	49.8768

90% *ee*



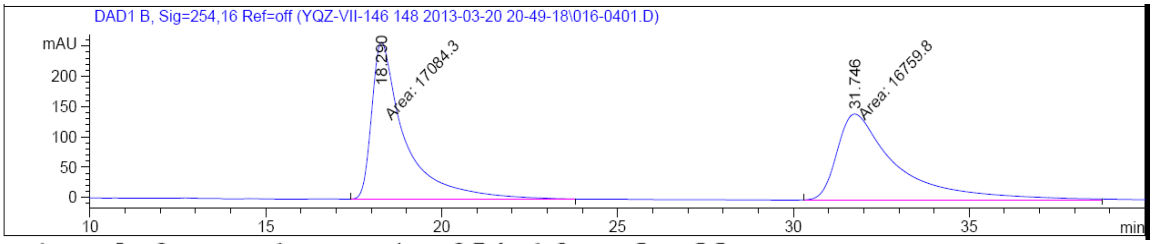
Signal 1: DAD1 A, Sig=272,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.083	MM	0.9707	1.57456e5	2703.55884	95.1095
2	25.904	MM	0.9367	8096.27344	144.05927	4.8905



4 R = 2,4-Cl_2-benzoyl

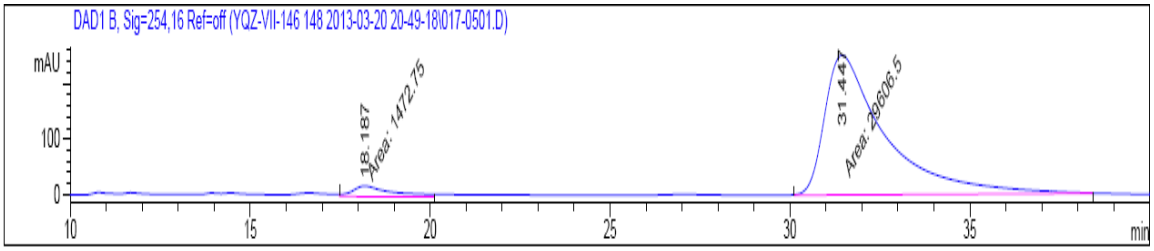
Racemic sample:



Signal 2: DAD1 B, Sig=254,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.290	MM	1.0987	1.70843e4	259.16397	50.4794
2	31.746	MM	1.9674	1.67598e4	141.97903	49.5206

90% *ee*

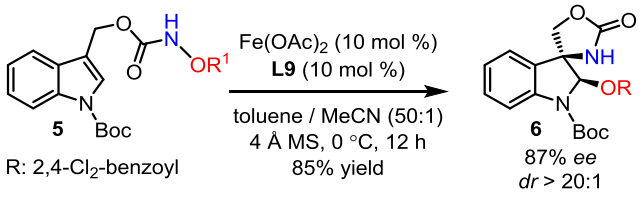


Signal 2: DAD1 B, Sig=254,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.187	MM	1.2973	1472.75427	18.92053	4.7387
2	31.447	MM	1.9620	2.96065e4	251.49319	95.2613

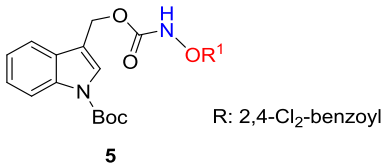
3.2.5 Asymmetric Aminohydroxylation of an N-Boc Indole and Product Derivatization

3.2.5.1 Asymmetric Aminohydroxylation of an N-Boc Indole



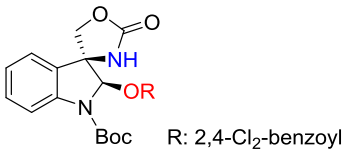
Scheme 53. Asymmetric Aminohydroxylation of an N-Boc Indole

Procedure for asymmetric aminohydroxylation of an *N*-Boc indole: To a flame-dried vial were added 4Å MS (50 mg), $Fe(OAc)_2$ (0.004 mmol) together with ligand **L9** (0.004 mmol). After evacuation upon oil pump and refill with argon three times, anhydrous and degassed toluene/MeCN (50:1, 1.5 mL) co-solvent was added. The obtained suspension was stirred vigorously at room temperature for 30 min before the substrate **5** (19 mg, 0.04 mmol) in the aforementioned co-solvent (0.5 mL) was added in one portion. The reaction system was stirred 0 ^{o}C for 12 h when all the starting material was fully consumed. Saturated $NaHCO_3$ aqueous solution was added to quench the reaction, and the aqueous phase was extracted with DCM three times. The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (hexane: THF = 4:1) to give the desired aminohydroxylation product **6** (16 mg, 85% yield).



***tert*-Butyl 3-(((((2,4-dichlorobenzoyl)oxy)carbamoyl)oxy)methyl)-1H-indole-1-carboxylate (5):** ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.44 (s, 1H), 8.17 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.71 (s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.52 (s, 1H), 7.39-7.25 (m, 3H),

5.43 (s, 2H), 1.69 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 163.7, 156.3, 149.4, 139.9, 135.7, 132.8, 131.2, 129.0, 127.2, 126.2, 124.9, 124.6, 122.9, 119.1, 115.3, 114.5, 84.1, 60.5, 28.1; IR ν_{max} (neat)/cm^{-1}: 3255 (w), 1733 (s), 1370 (m), 1087 (s), 731 (m); HRMS (ESI) calculated for $C_{22}H_{19}Cl_2N_2O_6$ [M - H]$^-$: 477.0620, found: 477.0610.



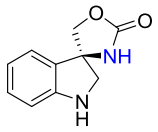
6

***tert*-Butyl (2*R*,3*S*)-2-((2,4-dichlorobenzoyl)oxy)-2'-oxospiro[indoline-3,4'-oxazolidine]-1-carboxylate (6):** The sample was analyzed by Chiral HPLC analysis and determined to be 87% *ee* (Chiralcel AD-H, 1.0 mL/min, 254 nm, 20% *i*-PrOH in hexane, t_r (minor) = 4.58 min, t_r (major) = 8.56 min). $[\alpha]_D^{20}$ = 44.7^o (c = 2.1, DCM). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.81 (d, *J* = 8.4 Hz, 1H), 7.47 (s, 1H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.32 (dd, *J* = 1.2 Hz, 8.4 Hz, 1H), 7.17 (t, *J* = 7.2 Hz, 1H), 6.96 (s, 1H), 6.36 (s, 1H), 4.71 (d, *J* = 9.2 Hz, 1H), 4.29 (d, *J* = 9.2 Hz, 1H), 1.52 (t, *J* = 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 163.2, 158.3, 150.8, 140.9, 139.2, 135.1, 133.0, 131.2, 127.2, 126.8, 124.4, 123.5, 115.2, 87.2, 83.4, 75.3, 28.2; IR ν_{max} (neat)/cm^{-1}: 3256 (w), 1765 (s), 1721 (s), 1379 (m), 765 (m); HRMS (ESI) calculated for $C_{22}H_{19}Cl_2N_2O_6$ [M - H]$^-$: 477.0620, found: 477.0625.

3.2.5.2 N-Boc Indole Product Derivatization

Scheme 54. Synthesis of Amino Indolane

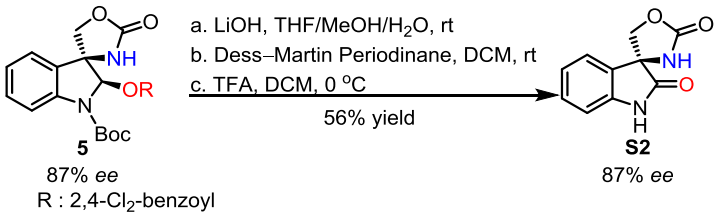
Procedure for Amino Indolane (6) Synthesis: 6 (0.04 mmol, 19 mg) was dissolved in DCM (2 ml), to which Et_3SiH (0.4 mmol, 63.0 μL) was then added, followed by addition of $BF_3{\cdot}Et_2O$ (0.12 mmol, 15μL) at -78 ℃. The mixture was stirred overnight and allowed to warm to 0 ^oC. Then DCM was added and the organic phase was washed with water. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed under vacuum and the residue was purified by silica gel flash column chromatography (hexane/EtOAc = 1:1) to afford the 3-amino indolane **S1** (13 mg, 66% overall yield).



S1

(*R*)-Spiro [indoline-3,4'-oxazolidin]-2'-one (S1): The sample was analyzed by Chiral HPLC analysis and determined to be 86% *ee* (Chiralcel AD-H, 1.0 mL/min, 254 nm, 10% EtOH in hexane, t_r (minor) = 51.76 min, t_r (major) = 72.76 min). $[\alpha]_D^{20}$ = -52.1^o (c = 0.19, DCM). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.31 (d, J = 7.6 Hz, 1H), 7.18 (t, J = 7.2 Hz, 1H), 6.86 (t, J = 7.2 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 4.50 (AB, 2H), 3.65 (AB, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 159.7, 150.6, 129.7, 129.3, 122.9, 119.7, 110.9, 76.2, 65.7, 58.3; IR ν_{max} (neat)/cm^{-1}: 3331 (w), 1740 (s), 1609 (m), 1387 (m), 754 (w).

3.2.5.3 Synthesis of Amino Oxindoles

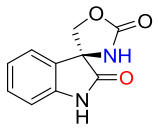


Scheme 55. Synthesis of Amino Oxindoles

Procedure for Synthesis of Amino Oxindoles (S2): At room temperature, LiOH (0.11 mmol, 2.46mg) was added to a solution of **5** (0.1 mmol) in THF/MeOH/H_2O (8/1/1, 2.0 mL). After stirring for 1.0 h, the reaction was concentrated *in vacuo*. Quick purification of the residue by a short flash chromatography (hexane/EtOAc) affords the crude hydroxyl oxazolidinone intermediate.

To a solution of the hydroxyl oxazolidinone intermediate obtained above in Dess−Martin Periodinane (0.22 mmol, 93 mg), $NaHCO_3$ (1.0 mmol, 84 mg) were added and the mixture was stirred for 10 h at room temperature before water was added. The resulting mixture was extracted with DCM three times, and the combined organic layers were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by silica gel flash column chromatography (hexane/EtOAc) to afford the oxindole intermediate.

To a solution of the oxindole intermediate obtained above in DCM (1.0 mL), TFA (1.0 mmol, 76 uL) was added and the mixture was stirred for 2 h at 0 ^oC before saturated $NaHCO_3$ aqueous solution was added. The resulting mixture was extracted with DCM for three times, and the combined organic layers were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. After being concentrated *in vacuo*, the residue was purified by silica gel flash column chromatography (hexane/EtOAc) to afford the amino oxindole product **S2** (11 mg, 56% overall yield).

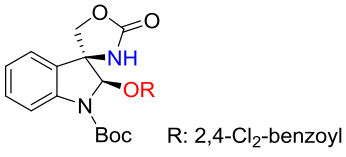


S2

(*S*)-Spiro [indoline-3,4'-oxazolidine]-2,2'-dione (S2): The sample was analyzed by Chiral HPLC analysis and determined to be 87% *ee* (Chiralcel AD-H, 1.0 mL/min, 254 nm, 20% *i*-PrOH in hexane, t_r (minor) = 13.12 min, t_r (major) = 7.08 min). $[\alpha]_D^{20} = 6.0^o$ (c = 0.05, DCM).

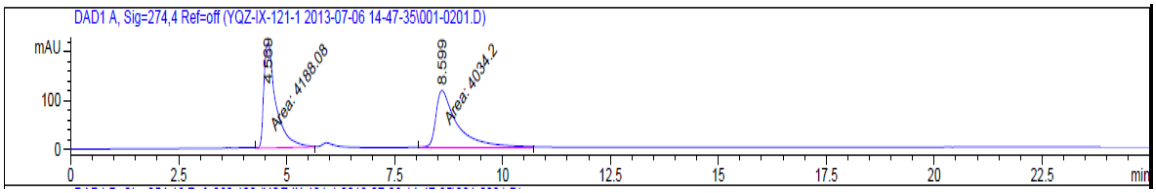
^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.48 (d, J = 7.6 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 4.55 (AB, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 130.3, 128.1, 124.0, 123.0, 110.3, 72.7; IR ν_{max} (neat)/cm^{-1}: 3250 (w), 1725 (s), 1620 (m), 1471 (m), 752 (m); HRMS (ESI) calculated for $C_{10}H_7N_2O_3$ [M - H]$^-$: 203.0457, found: 203.0451.

3.2.5.4 HPLC Data



6

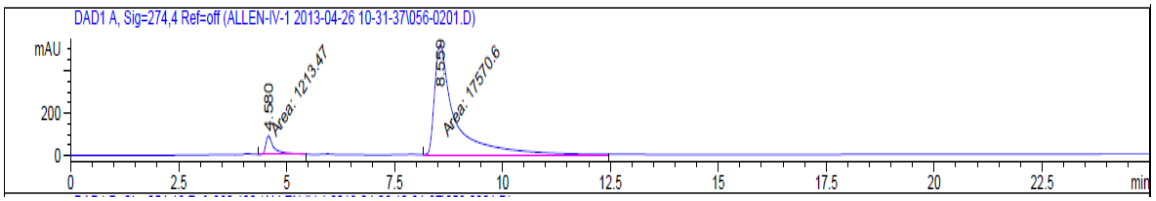
Racemic sample:



Signal 1: DAD1 A, Sig=274,4 Ref=off

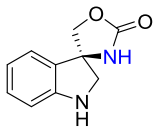
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.569	MM	0.3243	4188.07959	215.25876	50.9358
2	8.599	MM	0.5773	4034.19727	116.46326	49.0642

87% *ee*



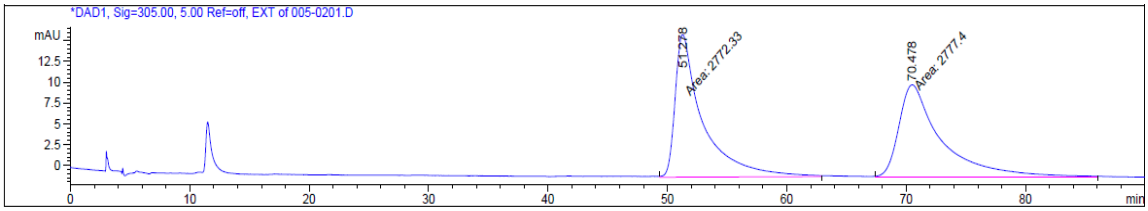
Signal 1: DAD1 A, Sig=274,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.580	MM	0.2279	1213.47314	88.75775	6.4601
2	8.559	MM	0.5640	1.75706e4	519.25574	93.5399



S1

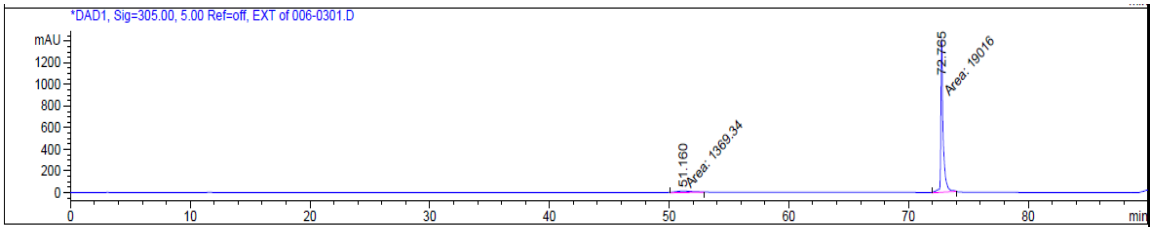
Racemic sample:



Signal 3: DAD1, Sig=305.00, 5.00 Ref=off, EXT
Signal has been modified after loading from rawdata file!

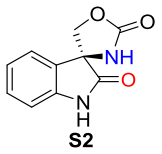
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	51.278	MM	2.6914	2772.32690	17.16756	49.9543
2	70.478	MM	4.1618	2777.39600	11.12248	50.0457

86% *ee*



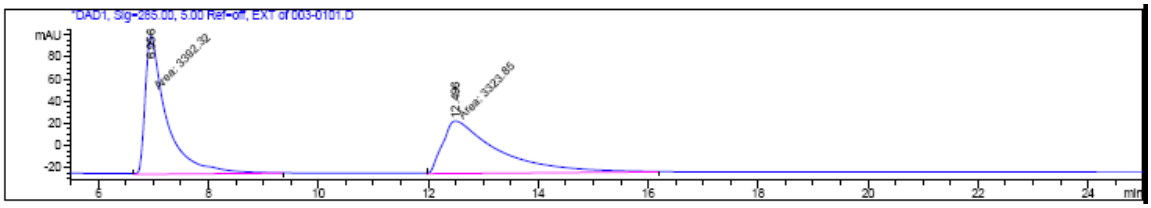
Signal 3: DAD1, Sig=305.00, 5.00 Ref=off, EXT
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	51.160	MM	1.7353	1369.34412	13.15154	6.7173
2	72.765	MM	0.2236	1.90160e4	1417.43347	93.2827



S2

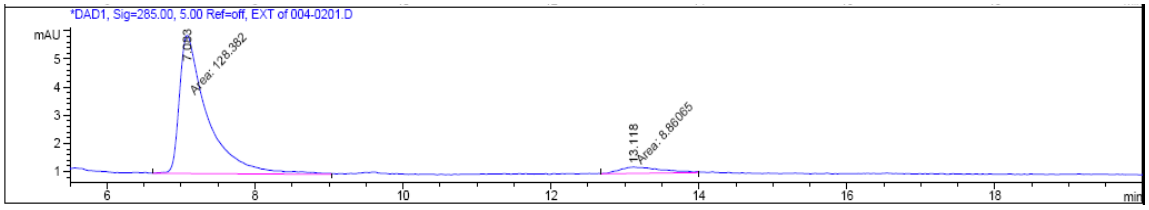
Racemic sample:



Signal 4: DAD1, Sig=285.00, 5.00 Ref=off, EXT
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.956	MM	0.4523	3392.31934	124.99969	50.5098
2	12.496	MM	1.1691	3323.84546	47.38362	49.4902

87% *ee*

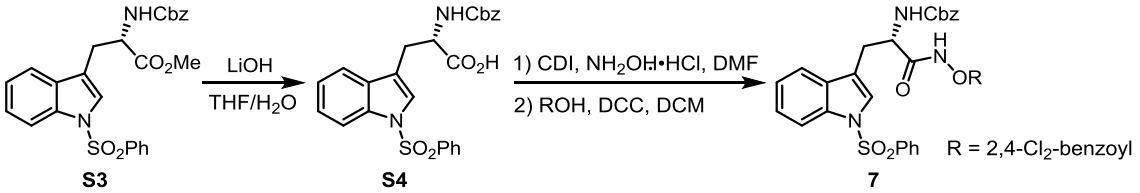


Signal 3: DAD1, Sig=285.00, 5.00 Ref=off, EXT
Signal has been modified after loading from rawdata file!

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.083	MM	0.4370	128.38167	4.89661	93.5438
2	13.118	MM	0.6480	8.86065	2.27912e-1	6.4562

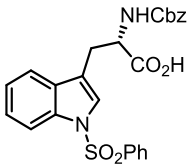
3.2.6 Iron-Catalyzed Aminohydroxylation of Functionalized Tryptophan

3.2.6.1 Preparation of Tryptophan Substrate



Scheme 56. Preparation of Tryptophan Substrate 5

Procedure for Substrate S4 Synthesis: LiOH (5.0 mmol) was added to a solution of L-tryptophan methyl ester **S3** (1.0 mmol) [2] in THF/H_2O (10 mL) and the mixture was stirred at room temperature for 10 h until the starting material was completely consumed. THF was removed under reduced pressure and the resulting residue was dissolved in DCM and washed with water three times. The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography (DCM/MeOH) to afford **S4** (423 mg, 86% yield).

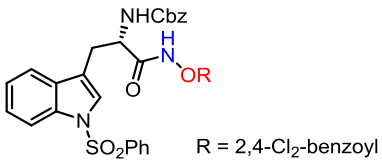


(*S*)-Methyl 2-(((benzyloxy)carbonyl)amino)-3-(1-(phenylsulfonyl)-1H-indol-3-yl)propanoate (S4) : ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.88 (brs, $1H_A$ + $1H_B$), 7.99 (d, J = 8.4 Hz, $1H_A$ + $1H_B$), 7.55 (s, $1H_A$), 7.51–7.39 (m, 4H), 7.31–7.29 (m, 11H), 7.20–7.14 (m, 3H), 6.87 (d, J = 7.6 Hz, $1H_B$), 5.50 (d, J = 7.6 Hz, $1H_A$), 5.12 (AB, $2H_A$), 4.91 (AB, $2H_B$), 4.79–4.74 (m, $1H_A$), 4.61–4.60 (m, $1H_B$), 3.36–3.06 (m, $2H_A$ + $2H_B$) ;^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 175.5, 155.9, 137.8, 135.9, 135.0, 133.7, 130.7, 130.4, 129.1, 128.5, 128.2, 128.0, 127.9, 126.6, 124.9, 124.6, 123.4, 119.4, 119.2, 117.2, 116.9, 113.6, 67.7, 67.2, 54.0, 53.7, 28.4, 27.4; IR ν_{max}

(neat)/cm^{-1}: 3067 (w), 1716 (s), 1367 (m), 1175 (s), 1047 (w).

Procedure for Substrate Tryptophan 7 Synthesis: At room temperature, CDI (2 mmol) was added to a solution of protected L-tryptophan **S4** (1.0 mmol) in DMF (10 mL). The reaction mixture was stirred for 30 min and then $NH_2OH{\cdot}HCl$ (4 mmol) was added. After being stirred for an additional 1.0 h at room temperature, H_2O (5 mL) was added and the reaction system was stirred for another 30 min, and then diluted with DCM (50 mL) and water (50 mL). The aqueous phase was extracted with DCM (50 mL) three times and the combined organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by short silica gel flash column chromatography (10% MeOH in DCM) to afford the hydroxyl carbamate intermediate (420 mg, 85% yield).

To a solution of the obtained hydroxyl carbamate (1.0 mmol) and 2, 4-dichlorobenzoyl acid (1.0 mmol) in DCM (10 mL), DCC (1.0 mmol) in DCM (3.0 mL) was added dropwise at 0 °C. After being stirred for 1.0 h, the reaction mixture was diluted by Et_2O (15 mL).The byproduct precipitated out and was removed by filtration. DCM was removed under vacuum and the residue was purified by silica gel flash column chromatography (30% EtOAc in hexanes) to afford **7** (480 mg, 72% yield).

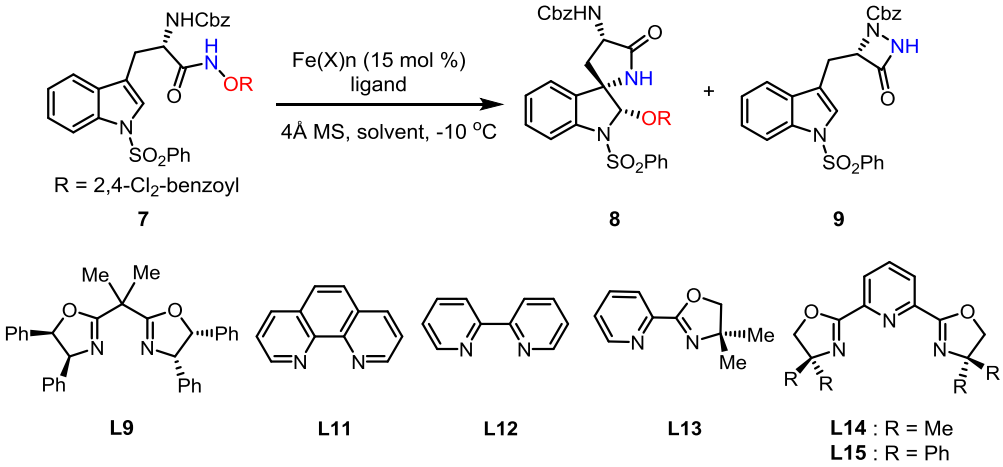


7

(*S*)-Benzyl (1-(((2,4-dichlorobenzoyl)oxy)amino)-1-oxo-3-(1-(phenylsulfonyl)-1H-indol-3-yl)propan-2-yl)carbamate (7) : ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 10.44 (brs, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 7.6 Hz, 3H), 7.58 (s, 1H), 7.49–7.41 (m, 3H), 7.35–7.21 (m, 9H), 7.16 (t, J = 7.6 Hz, 1H), 5.79 (d, J = 7.6 Hz, 1H), 5.02 (s, 2H), 4.76 (s, 1H), 3.22 (AB,

2H);^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 162.2, 139.9, 138.0, 135.7, 135.6, 135.1, 133.7, 132.9, 131.2, 130.4, 129.2, 128.5, 128.2, 128.0, 127.2, 126.7, 125.0, 124.4, 123.4, 119.3, 116.9, 113.7, 67.5, 52.2, 27.4; IR ν_{max} (neat)/cm^{-1}: 3285 (w), 1683 (s), 1374 (m), 1176 (s), 1081 (m); HRMS (ESI) calcd for $C_{32}H_{26}Cl_2N_3O_7S$ $[M+H]^+$: 666.0869, found 666.0865.

3.2.6.2 Reaction Discovery for Aminohydroxylation of Tryptophan Substrate

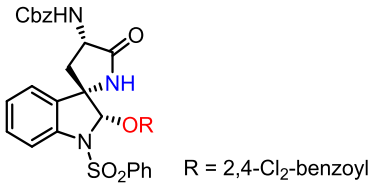


entry	ligand (mol %)	Fe(X)n (15 mol %)	solvent	time	conversion	yield (**8**)	yield (**9**)
1	**L11** (30)	$Fe(NTf_2)_2$	DCM	4 h	>95%	46%	21%
2	**L12** (30)	$Fe(NTf_2)_2$	DCM	5 h	>95%	< 5%	77%
3	**L13** (30)	$Fe(NTf_2)_2$	DCM	1 h	>95%	< 5%	85%
4	**L9** (30)	$Fe(NTf_2)_2$	DCM	2 h	>95%	< 5%	78%
5	*ent*-**L9** (30)	$Fe(NTf_2)_2$	DCM	2 h	>95%	< 5%	81%
6	**L14** (15)	$Fe(NTf_2)_2$	DCM	1 h	>95%	< 5%	81%
7	**L15** (15)	$Fe(NTf_2)_2$	DCM	1 h	>95%	< 5%	72%
8	**L11** (30)	$Fe(OAc)_2$	DCM	6 h	>95%	< 5%	51%
9	**L11** (30)	$Fe(NTf_2)_2$	MeCN	1 h	>95%	< 5%	52%
10	**L11**(15)	$Fe(NTf_2)_2$	Et_2O	8 h	>95%	< 5%	87%

Table 20. Reaction Conditions Screening for Aminohydroxylation of Tryptophan

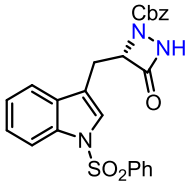
Procedure for Aminohydroxylation of 7: $Fe(NTf_2)_2$ (0.007 mmol) and 1,10-phenanthroline (0.014 mmol) were added to a flame-dried vial. After evacuation upon oil pump and refill with argon three times, anhydrous and degassed DCM (1.0 mL) was added. The resulting suspension was stirred vigorously at room temperature for 30 min and cooled down to -

10 ^{o}C. **7** (0.04 mmol) dissolved in anhydrous and degassed DCM (1.0 mL) was added dropwise to the reaction system, which was stirred at -10 ^{o}C for 4 h when all the starting material was fully consumed. Saturated $NaHCO_3$ aqueous solution was added to quench the reaction, and the aqueous phase was extracted with DCM three times. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (hexane: EtOAc = 2:1) to give **8** and **9** respectively.



8

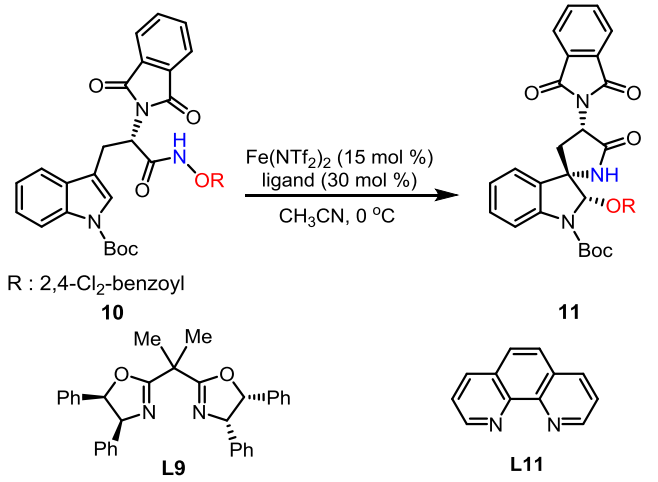
(2*S*,2'*S*,4'*S*)-4'-(Benzyloxycarbonylamino)-5'-oxo-1-(phenylsulfonyl)spiro[indoline-3,2'-pyrrolidine]-2-yl 2,4-dichlorobenzoate (8): by following the procedure above (0.04 mmol scale), the title compound **8** was obtained from **7** and isolated by a silica gel flash column as white foam (13 mg, 46% yield). $[\alpha]_D^{20}$ = -36.3^{o} (c = 0.8, DCM). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.69-7.57 (m, 3H), 7.49–7.34 (m, 9H), 7.24–7.16 (m, 4H), 6.74 (s, 1H), 5.96 (s, 1H), 5.35 (d, *J* = 8.4 Hz, 1H), 5.09 (s, 2H), 4.49-4.44 (m, 1H), 2.44–2.39 (m, 1H), 2.16–2.10 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 163.4, 155.8, 139.5, 139.48, 138.2, 136.0, 135.6, 134.0, 133.0, 131.5, 131.2, 130.9, 129.6, 128.6, 128.3, 128.1, 127.1, 126.9, 126.3, 125.5, 124.1, 114.4, 88.9, 67.1, 64.9, 51.3, 42.0. IR ν_{max} (neat)/cm^{-1}: 3362 (w), 1710 (s), 1366 (m), 1238 (m), 1173 (s); HRMS (ESI) calcd for $C_{32}H_{26}Cl_2N_3O_7S$ $[M+H]^+$: 666.0869, found 666.0868.



9

(*S*)-Benzyl 3-oxo-4-((1-(phenylsulfonyl)-1H-indol-3-yl)methyl)-1,2-diazetidine-1-carboxylate (9): by following the general procedure (0.04 mmol scale), the title compound **9** was obtained from **7** and isolated by a silica gel flash column as white foam (5 mg, 25% yield). $[\alpha]_D^{20}$ = -38.2° (c = 1.6, DCM). ^{1}H NMR (400 MHz, d_6-acetone, ppm): δ 8.02 (d, J = 8.4 Hz, 1H), 7.97-7.93 (m, 2H), 7.78 (s, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.63–7.59 (m, 1H), 7.52–7.47 (m, 3H), 7.39–7.26 (m, 6H), 5.69 (q, J = 7.6 Hz, 1H), 5.15–5.08 (m, 2H), 3.29 (d, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, d_6-acetone, ppm): δ 137.9, 135.1, 134.2, 130.8, 129.5, 128.4, 128.0, 127.9, 126.7, 124.9, 123.5, 119.8, 117.6, 113.6, 66.3, 63.2, 31.6. IR ν_{max} (neat)/cm^{-1}: 3306 (w), 2246 (s), 1716 (m), 1174 (s); MS (ESI) calcd for $C_{25}H_{21}N_3NaO_5S$ $[M+Na]^+$: 498.1, found 498.1.

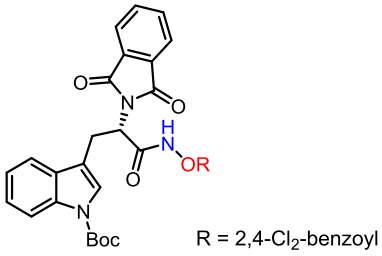
3.2.6.3 Reaction Discovery for Aminohydroxylation of Tryptophan Substrate



entry	ligand	time	conversion	yield	*dr*
1	**L11**	8 h	>95%	76%	1.7:1
2	**L9**	12 h	76%	43%	1.2:1
3	*ent*-**L9**	12 h	64%	37%	1:1

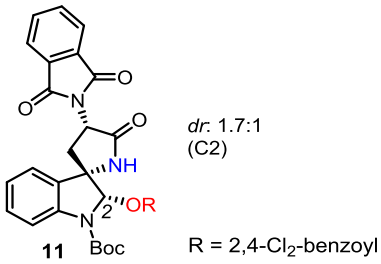
Table 21. Reaction Discovery for Aminohydroxylation of Tryptophan Substrate 10

Procedure for Aminohydroxylation of 10: $Fe(NTf_2)_2$ (0.007 mmol) and 1,10-phenanthroline (0.014 mmol) were added to a flame-dried vial. After evacuation with a vacuum pump and refill with argon three times, anhydrous and degassed CH_3CN (1.0 mL) was added. The resulting suspension was stirred vigorously at room temperature for 30 min and cooled down to 0 ^oC. **10** (0.04 mmol) dissolved in anhydrous and degassed CH_3CN (1.0 mL) was added dropwise to the reaction system, which was stirred at 0 ^oC for 8 h when all the starting material was fully consumed. Saturated $NaHCO_3$ aqueous solution was added to quench the reaction, and the aqueous phase was extracted with DCM three times. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (hexane: EtOAc = 2:1) to give **11**.



10

(*S*)-*tert*-Butyl 3-(3-(((2,4-dichlorobenzoyl)oxy)amino)-2-(1,3-dioxoisoindolin-2-yl)-3-oxopropyl)-1H-indole-1-carboxylate (10): white solid (mp: 155-157 ^oC**)** ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 10.47 (brs, 1H), 8.05 (d, J = 7.6 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.79-7.76 (m, 2H), 7.69-7.66 (m, 2H), 7.56 (d, J = 8.0 Hz, 2H), 7.46 (s, 1H), 7.42 (s, 1H), 7.31-7.16 (m, 3H), 5.42 (t, J = 8.0 Hz, 1H), 3.74 (d, J = 8.0 Hz, 2H), 1.58 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 167.9, 162.4, 149.4, 139.9, 135.8, 134.5, 133.0, 131.4, 129.7, 127.3, 124.7, 124.5, 124.3, 123.8, 122.7, 118.7, 115.3, 115.0, 83.6, 52.8, 33.7, 28.1. IR ν_{max} (neat)/cm^{-1}: 3350 (w), 1717 (s), 1372 (m), 878 (m); HRMS (ESI) calcd for $C_{31}H_{25}Cl_2N_3O_7Na$ $[M+Na]^+$: 644.0967, found 644.0958.



(2*S*, 2'*S*, 4'*S*)-*tert*-Butyl 2-((2,4-dichlorobenzoyl)oxy)-4'-(1,3-dioxoisoindolin-2-yl)-5'-oxospiro[indoline-3,2'-pyrrolidine]-1-carboxylate (11): by following the procedure above (0.04 mmol scale), the title compound **11** was obtained from **10** and isolated by a silica gel flash column as white solid (mp: 183-185 ^{o}C, 19 mg, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.78-7.76 (m, 8H), 7.68 (d, J = 7.6 Hz, 1H), 7.47 (s, 1H), 7.40-7.30 (m, 4H), 7.20 (t, J = 8.0 Hz, 1H), 6.91 (s, 1H), 6.46 (s, 1H) (6.38 (s, 1H, minor diastereomer)), 5.39 (d, J = 10.0 Hz, 1H) (5.28 (d, J = 10.0 Hz, 1H, minor diastereomer)), 2.91 (t, J = 8.0 Hz, 1H) (3.14 (t, J = 8.4 Hz, 1H, minor diastereomer)), 2.76 (t, J = 12.8 Hz, 1H) (2.61 (t, J = 9.6 Hz, 1H, minor diastereomer)), 1.52 (s, 9H) (1.55 (s, 5H, minor diastereomer)); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 172.0, 171.9, 171.5, 167.3, 163.8, 162.6, 151.0, 139.9, 139.3, 139.1, 135.2, 135.0, 133.2, 132.9, 131.24, 131.2, 130.6, 130.4, 127.3, 124.6, 124.2, 123.9, 123.8, 123.7, 122.1, 115.4, 114.8, 88.9, 88.1, 83.3, 64.1, 63.8, 48.6, 48.1, 39.0, 38.8, 28.2. IR ν_{max} (neat)/cm^{-1}: 3340 (w), 1717 (s), 1040 (m), 880 (m); HRMS (ESI) calcd for $C_{31}H_{25}Cl_2N_3O_7Na$ $[M+Na]^+$: 644.0967, found 644.0959.

3.2.7 X-ray Crystallographic Analysis for Product Absolute Stereochemistry Determination

Please refer to **Appendix E** for further details.

3.3 RESULTS

Despite these important achievements, the catalytic asymmetric aminohydroxylation of indoles with synthetically useful *ee* has remained a challenge.[57] Likewise, iron-catalyzed olefin

aminohydroxylation is also a less-explored process;[14b, 14d, 14e, 62] however, Yoon recently discovered an iron-catalyzed olefin aminohydroxylation with sulfonyl oxaziridines.[35-36] We have recently reported an iron-catalyzed intramolecular olefin aminohydroxylation and the mechanistic studies revealed that an iron-nitrenoid is a possible intermediate in the selective atom transfer reaction.[63] Herein, we describe our latest discovery: an iron(II)-catalyzed asymmetric intramolecular aminohydroxylation of indoles. In this reaction, the iron catalyst diastereo- and enantioselectively transfer the *N* and *O* group of the hydroxylamine to a variety of indoles (*dr* > 20:1, *ee* up to 99%). Simple product derivatization provides both amino oxindoles and amino indolanes in their enantioenriched forms.

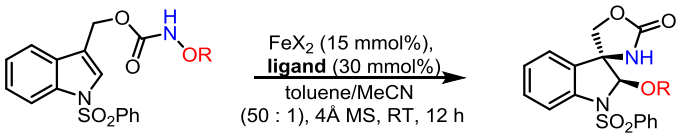
3.3.1 Iron Catalyst Discovery

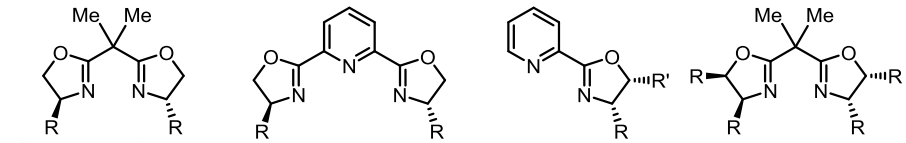
3.3.1.1 Iron(II)-Catalyzed Racemic Reaction

We initiated the catalyst discovery with a model substrate **1** and extensive optimization revealed that the $FeSO_4$–1,10-phenanthroline complex catalyzes an efficient racemic indole aminohydroxylation reaction affording product **2** as a single diastereomer (Table **9**).

3.3.1.2 Iron(II)-Catalyzed Asymmetric Reaction

With the optimized racemic reaction in hand, we set out to search for chiral ligands that effectively promote enantioselective indole aminohydroxylation with iron(II) complexes (Table **22**). Since $FeSO_4$ is poorly soluble in nonpolar solvents such as toluene, we selected $Fe(OTf)_2$ as the iron salt for chiral ligand discovery. Extensive experimentation revealed that a toluene–MeCN (50:1) mixture is crucial for high enantioselectivity. Under these conditions, we systematically inspected a series of chiral bisoxazoline (BOX) and pyridine–oxazoline (PyBOX) hybrid ligands.[37b, 45a, 45b, 45d, 64]





entry[a]	R'	FeX_2	L	yield[b]	*ee*[c]
1	2,4-Cl_2-benzoyl	$Fe(OTf)_2$	**L1**	22%	0%
2	2,4-Cl_2-benzoyl	$Fe(OTf)_2$	**L2**	25%	31%
3	2,4-Cl_2-benzoyl	$Fe(OTf)_2$	**L3**	58%	77%
4[d]	2,4-Cl_2-benzoyl	$Fe(OTf)_2$	**L4**	48%	-86%
5	2,4-Cl_2-benzoyl	$Fe(OTf)_2$	**L5**	15%	32%
6	2,4-Cl_2-benzoyl	$Fe(OTf)_2$	**L6**	33%	22%
7	2,4-Cl_2-benzoyl	$Fe(OTf)_2$	**L7**	21%	37%
8	2,4-Cl_2-benzoyl	$Fe(OTf)_2$	**L8**	25%	61%
9	2,4-Cl_2-benzoyl	$Fe(OTf)_2$	**L9**	65%	87%
10	2,4-Cl_2-benzoyl	$Fe(OTf)_2$	**L10**	50%	81%
11	4-CO_2-Me-benzoyl	$Fe(OTf)_2$	**L9**	62%	87%
12	4-CF_3-benzoyl	$Fe(OTf)_2$	**L9**	65%	77%
13	4-Cl-benzoyl	$Fe(OTf)_2$	**L9**	58%	78%
14	3,5-$(CF_3)_2$-benzoyl	$Fe(OTf)_2$	**L9**	75%	75%
15	2,4-Cl_2-benzoyl	$Fe(NTf_2)_2$	**L9**	67%	79%
16	2,4-Cl_2-benzoyl	$FeCl_2$	**L9**	63%	86%
17	2,4-Cl_2-benzoyl	$FeBr_2$	**L9**	52%	75%
18	2,4-Cl_2-benzoyl	$Fe(OAc)_2$	**L9**	67%	90%

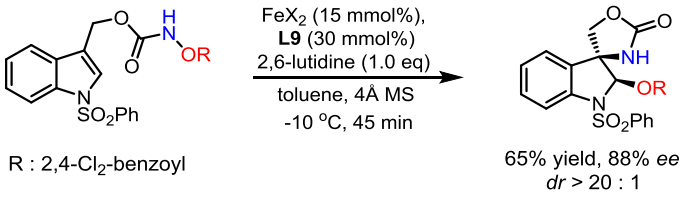
[a]Reactions were carried out under argon in 0.025 M toluene/MeCN (50:1) mixture; catalyst complexes were formed by premixing $Fe(X)_2$ and ligands for 40 min. [b]Isolated yield. [c]ee was measured by HPLC analysis with chiral stationary phase. [d]The sense of enantioinduction in entry 4 is opposite to that of other entries.

Table 22. Catalyst Discovery for the Asymmetric Indole Aminohydroxylation

We observed that the $Fe(OTf)_2$–*i*PrBOX **L1** complex fails to induce any enantioselectivity (entry 1); however, the $Fe(OTf)_2$–*t*BuBOX **L2** complex is capable of asymmetric induction (entry 2, 31% *ee*). The change from **L2** to PhBOX **L3** correlates with both enhanced reactivity and enantioselectivity (entry 3, 58% yield, 77% *ee*). Surprisingly, a relatively minor modification to the ligand's structure (from PhBOX **L3** to BnBOX **L4**) leads to asymmetric induction in the opposite sense (entry 4, 48% yield, −86% *ee*). We, therefore, tested

PyBOX and pyridine-oxazoline hybrid ligands **L5**–**L8** and determined that they are inferior to **L3** and **L4** (entries 5–8, *ee* up to 61%). Further screening of tetrasubstituted chiral BOX ligands (**L9**–**L10**) revealed that the $Fe(OTf)_2$–**L9** complex catalyzes the indole aminohydroxylation with further enhanced *ee* (entry 9, 65% yield, 87% *ee*). Knowing that aromatic interaction may be important for asymmetric induction,[65] we carried out electronic tuning experiments on the benzoyl protecting group. We discovered that the 4-Cl, 4-CF_3, and 3,5-$(CF_3)_2$ substituents result in decreased *ee* while the 4-CO_2Me group maintains the similar *ee* (entries 11–14 compared with entry 9). We also observed that hydrolytically more robust $Fe(NTf_2)_2$[45e] promotes the reaction with a slightly increased yield yet decreased *ee* (entry 15, 67% yield, 79% *ee*). Concordantly, we discovered that both $FeCl_2$ and $FeBr_2$ promote less selective reactions with **L9** (entries 16–17); however, the $Fe(OAc)_2$–**L9** complex manages to increase the *ee* to 90% in 12 h (entry 18).

3.3.1.3 N-Donor Effect

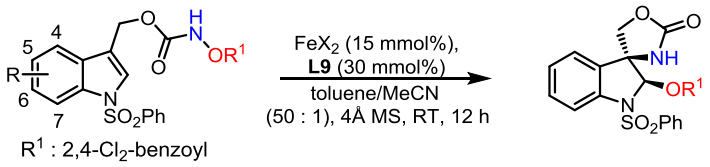


Scheme 57. Iron(II)-Catalyzed Indole Aminohydroxylation Accelerated by 2,6-Lutidine

In order to search for a more reactive yet highly selective catalyst, we inspected a variety of additives with bulky N-donor ability.[66] Extensive optimization revealed that 2,6-lutidine (1.0 equiv) significantly accelerates the $Fe(OTf_2)$–**L9** catalyzed reaction in toluene with a slight increase in enantioselectivity (Scheme **57**, full conversion in 45 min at −10 °C, 65% yield, 88% *ee*). This discovery offers us an opportunity to expand the substrate scope and includes substrates that have low reactivity in $Fe(OAc)_2$-catalyzed reactions.

3.3.2 Substrate Scope

To explore the scope and limitation of the aforementioned method, we applied the optimized reaction conditions to a variety of substituted indoles (Table **23**). We observed that 5-methylindole is an excellent substrate for $Fe(OAc)_2$-catalyzed asymmetric aminohydroxylation (AA) (entry 2, 94% *ee*). Likewise, the $Fe(OTf)_2$–**L9**–lutidine complex enantioselectively converts a 5-methoxy indole to its corresponding hydroxyl oxazolidinone (entry 3, 93% *ee*). We also discovered that 6-methyl-, bromo-, and chloro-substituents are all well-tolerated in the $Fe(OAc)_2$-catalyzed indole AA, which thereby offers versatile handles for further transformation (entries 4–6, 91–99% *ee*). Further exploration revealed that 6-phenyl indole is an excellent substrate for $Fe(OTf)_2$-catalyzed AA (entry 7, 91% *ee*) and that 7-methyl indole participates in the $Fe(OAc)_2$-catalyzed AA with acceptable *ee* (entry 8, 88% *ee*). However, we observed that the *ee* for aminohydroxylation of 4-bromo indole is significantly lower than other substrates (entry 9, 74% *ee*), which suggests that 4-H may be important for asymmetric induction.



entry[a]	R	yield[b]	*ee*[c]
1	H	67%	90%
2[d]	5-Me	72%	94%
3[d,e]	5-OMe	75%	93%
4	6-Me	65%	95%
5	6-Br	64%	91%
6	6-Cl	70%	99%
7[e]	7-Ph	65%	91%
8[d]	7-Me	62%	85%
9	4-Br	67%	74%

[a]Reactions were carried out under argon in 0.025 M toluene/MeCN (50:1) mixture unless stated otherwise. [b]Isolated yield, and 3-indole aldehydes were isolated (ca. 15%) as the side product. [c]ee was measured by HPLC analysis with chiral stationary phase. [d]R^1 = 4-CO_2Mebenzoyl. [e]Reactions were carried out under argon at 0.025 M toluene at 10 °C for 4 h. $Fe(OTf)_2$ (15 mol %) and **L9** (30 mol %) were applied as the catalyst and 2,6-lutidine (1.0 equiv) was used as the additive.

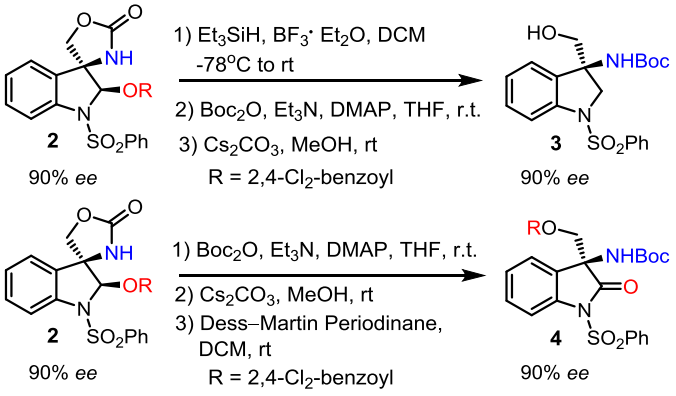
Table 23. Substrate Scope for the Asymmetric Indole Aminohydroxylation

3.3.3 Synthetic Transformations

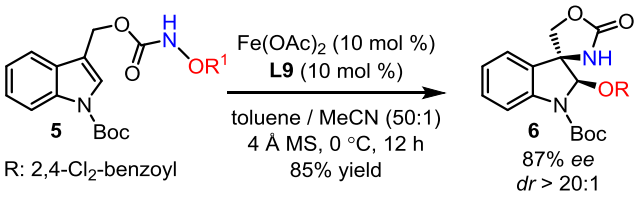
The enantio-enriched hydroxyl oxazolidinone **2** can be readily converted to either amino indolane **3** or amino oxindole **4** without erosion of the *ee* with three-step procedures (Scheme **58A**). The *N*-sulfonyl protected amino oxindole motif is of interest in medicinal chemistry because it is present in SSR-149415, a medicine for the treatment of anxiety and depression. In order to develop an easy entry to both unprotected amino indolanes and oxindoles, we explored the aminohydroxylation of an *N*-Boc protected indole **5** (Scheme **58B**). We observed that $Fe(OAc)_2$–**L9** complex catalyzes the efficient aminohydroxylation of **5** with an even lower catalyst loading, affording product **6** with excellent yield (10 mol% catalyst, 85% yield, *dr* > 20:1, 87% *ee*).

We further observed that the $Fe(NTf_2)_2$–phenanthroline complex catalyzes the aminohydroxylation of a protected tryptophan **7** to afford a single diastereomeric hydroxyl oxazolidinone **8** (full conversion, 46% yield, Scheme **58C**); interestingly, the aminohydroxylation occurs from the α face of tryptophan. In addition, we also isolated diazetidinone **9** (25% yield), a side product that is possibly derived from an N–H insertion reaction of the putative iron-nitrenoid intermediate. We, therefore, applied the same catalyst to another fully protected tryptophan **10** and observed the efficient aminohydroxylation afford **11**.

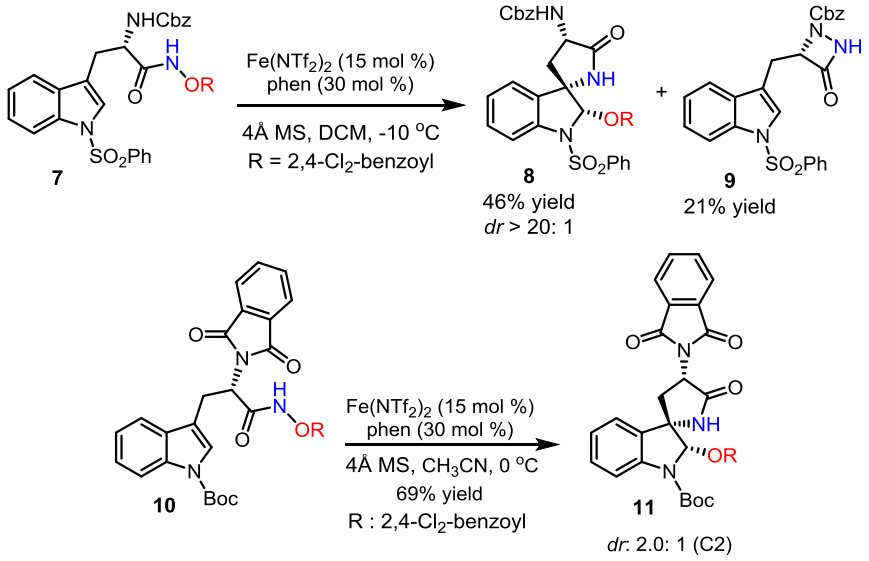
A) synthetic transformation of the product: amino indolanes and amino oxindoles



B) asymmetric aminohydroxylation of an N-Boc indole



C) aminohydroxylation of tryptophan



Scheme 58. Product Synthetic Transformation and the Iron(II)-Catalyzed AA of Tryptophan

3.4 CONCLUSIONS

In conclusion, we have discovered an asymmetric intramolecular indole aminohydroxylation catalyzed by iron(II)–chiral BOX complexes. This enantioselective process enables the facile asymmetric synthesis of biologically relevant 3-amino oxindoles and 3-amino indolanes. Our current research focuses on the application of this method in medicinal agent synthesis and a better understanding of the origin for asymmetric induction.

4 CHAPTER IV IRON CATALYZED DIRECT DIAZIDATION FOR A BROAD RANGE OF OLEFINS

4.1 INTRODUCTION

4.1.1 Naturally Occurring Molecules

Since the first discovery of organic azides more than 140 years by Peter Grieß,[67] it has been broadly applied in numerous syntheses of important classes of organic compounds. Particularly in more recent years, a varied utility of organic azides was developed due to its good accessibility, such as organic functional group transformations in industrial and pharmaceutical areas, the synthesis of heterocycles and the well-known "Click Chemistry". In spite of the explosive property of azide compounds, a vast utility of azido group in a late stage diversification of commercially available drug candidates, biomedical probes, as well as molecule libraries received considerable attentions.[68]

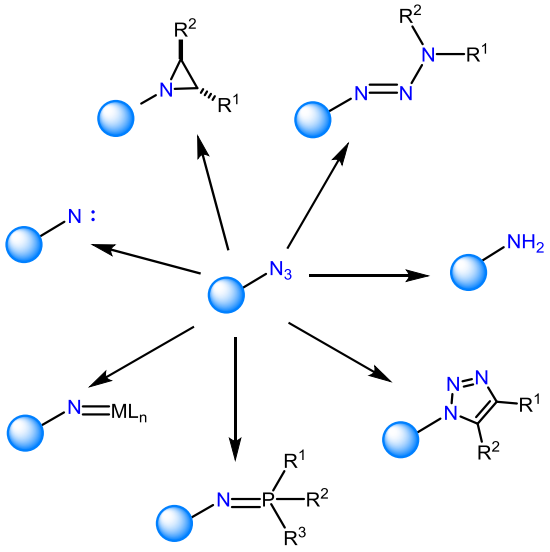


Figure 6. Important Transformations of Organic Azides

More importantly, we have witnessed the power and achievements of selective nitrogen-atom-transfer for olefin functionalization due to their generation of high-value chemicals from readily available hydrocarbons or petrochemicals. Among the blossoming of C-H activations as well as olefin functionalization processes by azido-group transfer, catalytic olefin diazidation has emerged with unique value for a few reasons.[67-69] First and foremost, vicinal diamines are important structural motifs that widely exist in naturally occurring molecules as shown in Figure **7**. Thus, this reaction provides an easy access to affording synthetically important vicinal primary diamines which are difficult to obtain with the currently existing olefin diamination methods.[70] Next, it can also rapidly convert olefins into a variety of probes for the robust azide–alkyne click chemistry, which has given organic azides irreplaceable roles in biological and material sciences.[69a] Therefore, searching for a general, yet novel selective olefin diazidation method has been an attracting research area and a variety of methods for certain limited types of olefins have been developed.[71]

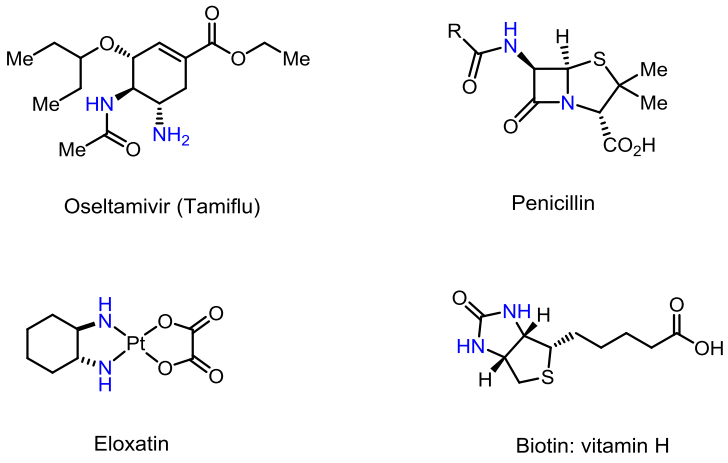
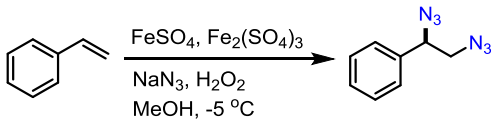


Figure 7. Compounds Containing the Vicinal Diamine Motif

4.1.2 Fe(II)/Fe(III)-Mediated Reactions

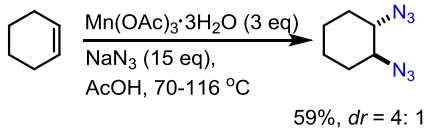
Minisci developed a Fe(II)/Fe(III)-mediated stoichiometric approach, with hydrogen peroxide and NaN_3, specifically for styrenyl olefins. In his case, the yield of diazide product is significantly affected by the oxidant type. However, this method is incompatible with nonstyrenyl olefins.[71i]



Scheme 59. Fe(II)/Fe(III)-Mediated Diazidonation of Alkenes

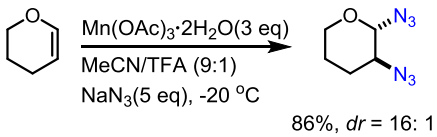
4.1.3 Mn(III)-Mediated Reactions

Fristad and co-workers reported a Mn(III)-mediated stoichiometric method only for nonfunctionalized aliphatic olefins with a large excess of NaN_3 in acetic acid at 110 °C. The rate enhancement evidences that ligand transfer oxidation happened in the presence of alkenes rather than the participation of the free azido radical.[71c]



Scheme 60. Mn(III)-Mediated Diazidation of Alkenes

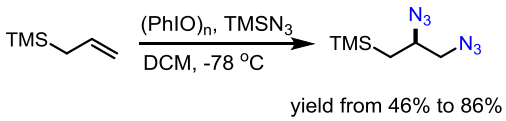
Later on, Snider subsequently reported a key improvement of Fristad's procedure by using a mixture of MeCN/TFA at −20 °C.[71l] This modified procedure is effective for acid-sensitive substrates, such as glycal; however, it is unsuitable for acyclic aliphatic olefins.



Scheme 61. Modified Mn(III)-Mediated Diazidation of Alkenes

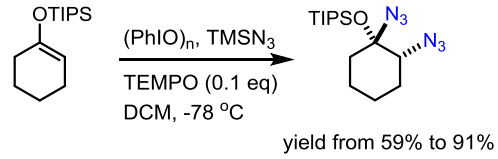
4.1.4 Aryl-λ^3-Iodanes Mediated Reactions

The group of Arimoto reported (PhIO)n/$TMSN_3$-mediated method specifically for electron-rich allyl silanes in DCM at −78 °C to room temperature to afford vicinal diazide in the absence of BF_3.Et_2O with good yields.[71a]



Scheme 62. $(PhIO)_n$-Mediated Diazidation of Alkenes

More recently, Magnus discovered that treatment of silyl enol ether with (PhIO)n/$TMSN_3$ with the addition of catalytic amount of the stable radical TEMPO can boost the high yield of the corresponding diazide product.[71h]



Scheme 63. TEMPO-Mediated Diazidation of Alkenes

These methods have been valuable for synthetic chemistry; however, significant gaps still exist for this important transformation. First, a general and selective catalytic method that is compatible with a broad range of both unfunctionalized and highly functionalized olefins has yet to be developed. Second, a diastereoselective method for internal olefins has not yet been reported. Furthermore, a new diazidation reaction which proceeds through a new selective pathway under mild reaction conditions (thus avoiding both heating and cryogenic cooling) has yet to be discovered.

4.2 EXPERIMENT

4.2.1 General Procedure

General Procedures. All reactions were performed in oven-dried or flame-dried round-bottom flasks and vials. Stainless steel syringes and cannula were used to transfer air- and moisture-sensitive liquids. Flash chromatography was performed using silica gel 60 (230−400 mesh) from Sigma–Aldrich.

Materials. Commercial reagents were purchased from Sigma–Aldrich, Fluka, EM Science, and Lancaster and used as received. All solvents were used after being freshly distilled unless otherwise noted.

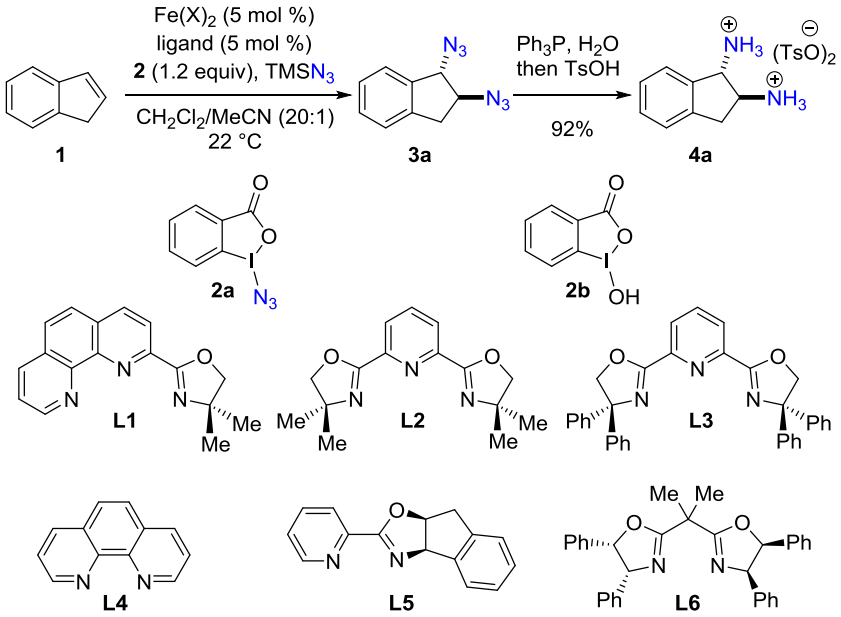
Instrumentation. Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Bruker UltraShield–400 (400 MHz). Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to the NMR solvent residual peak ($CHCl_3$ δ 7.26). Chemical shifts for carbons are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$ δ 77.0). Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz), and integration. The mass spectroscopic data were obtained at the Georgia State University mass spectrometry facility using a Micromass Platform II single quadrupole instrument. Infrared (IR) spectra were obtained using a Perkin Elmer Spectrum 100 FT-IR spectrometer. Data are represented as follows: frequency of absorption (cm^{-1}) and absorption strength (s = strong, m = medium, w = weak).

Abbreviations Used: EtOH–ethanol, EtOAc–ethyl acetate, THF–tetrahydrofuran, MeOH–methanol, Et_2O–diethyl ether, CH_2Cl_2–dichloromethane, TEA–triethylamine, MeCN–

acetonitrile, MS–molecular sieves, CDI–1,1′-carbonyldiimidazole, Troc–2,2,2-trichloroethoxycarbonyl, DCC–*N*,*N*′-dicyclohexylcarbodiimide, TLC–thin layer chromatography, Boc_2O–di-*tert*-butyl dicarbonate, DMAP−4-dimethylaminopyridine, $TBAN_3$–tetra-*n*-butylammonium azide, HATU−1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate.

4.2.2 Catalyst Discovery and Procedures for the Diazidation

4.2.2.1 Catalyst Discovery for the Iron-Catalyzed Indene Diazidation



Entry	$Fe(X)_2$	Ligand	**2**	$TMSN_3$ [equiv]	Time [h]	Yield[c] [%]	*dr*[c]
1[b]	$Fe(OTf)_2$	**L1**	**2a**	0	24.0	<5	NA
2	$Fe(OTf)_2$	**L1**	**2a**	1.5	1.0	81	3.7:1
3[b]	none	**none**	**2a**	1.5	1.0	<5	NA
4	$Fe(OTf)_2$	**L2**	**2a**	1.5	1.0	82	7.1:1
5	$Fe(OTf)_2$	**L3**	**2a**	1.5	1.0	85	8.5:1
6	$Fe(OTf)_2$	**L3**	**2b**	3.6	1.0	82	8.6:1
7	$Fe(NTf_2)_2$	**L3**	**2b**	3.6	1.0	78	8.0:1
8	$Fe(OAc)_2$	**L3**	**2b**	3.6	3.5	87	>20:1
9	$Fe(OAc)_2$	**L4**	**2b**	3.6	3.5	75	8:1
10[e]	$Fe(OAc)_2$	**L5**	**2b**	3.6	3.0	84	10:1
11[e]	$Fe(OAc)_2$	**L6**	**2b**	3.6	3.5	82	7:1

[a]Reactions were carried out under N_2 and then quenched with a saturated $NaHCO_3$ solution unless stated otherwise. Standard precautions with regard to handling $TMSN_3$ should be taken during the reaction workup. Reduction condition: PPh_3 (2.5 equiv), H_2O (5.0 equiv), THF, 50 °C, 2 h, then TsOH (2.5 equiv). [b]Conversion is < 5%. [c]Isolated yield; *dr* was measured by **^{1}H NMR** analysis. OTf: trifluoromethanesulfonate, NTf_2: trifluoromethanesulfonimide. [e]No significant *ee* was observed (*ee* <5%).

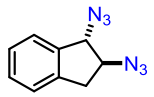
Table 24. Catalyst Discovery for the Iron-Catalyzed Indene Diazidation[a]

4.2.2.2 General Procedure for the Iron-Catalyzed Indene Diazidation

To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added an iron salt (0.02 mmol) and a ligand (0.02 mmol). After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (0.8 mL) and MeCN (0.2 mL) were added via a syringe and the mixture was stirred at room temperature for 10 min. To another flame-dried 3-dram vial (vial **B**) equipped with a stir bar was added **2a** or **2b** (0.48 mmol). This vial was evacuated and backfilled with N_2 three times and then anhydrous CH_2Cl_2 (3.0 mL) was added. Both vials were degassed with brief evacuation and then backfilled with N_2 twice. Subsequently, freshly distilled $TMSN_3$ (79 μL, 0.6 mmol or 190 μL, 1.44 mmol) and indene **1** (47 μL, 0.4 mmol) were added to vial **B**, followed by drop-wise addition of the catalyst solution in vial **A** at room temperature. The reaction was kept at the same temperature for the indicated time and then quenched with saturated $NaHCO_3$ solution (0.1 mL) and then further diluted with hexanes (5 mL). The mixture was stirred vigorously for 10 min and filtered through a short silica gel pad. The filtrate was further concentrated *in vacuo* and directly subject to *dr* analysis by ^{1}H NMR. The residue was further purified through a silica gel flash column (hexanes/Et_2O: from 200:1 to 50:1) to afford the indene diazide **3a** as colorless oil.

Warning: Standard precautions with regard to handling $TMSN_3$ should be taken during the reaction workup since an extra equivalent of $TMSN_3$ is used when **2b** is directly used as the terminal oxidant.

Since the C/N ratios for indene diazide are between 1 and 3, careful isolation and characterization of diazides was carried out under small-scale (<100 mg) conditions.

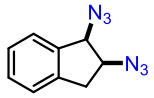


trans-**3a**

***trans*-1,2-Diazido-2,3-dihydro-1*H*-indene** (*trans*-**3a**). The major diastereomer *trans*-**3a** is a known compound: both the ^{1}H NMR and ^{13}C NMR data are in accordance with the literature data.[72]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67–6.68 (m, 4H), 4.77 (d, J = 5.6 Hz, 1H), 4.17 (dd, J = 12.8, 6.7 Hz, 1H), 3.35 (dd, J = 16.0, 7.3 Hz, 1H), 2.94 (dd, J = 16.0, 6.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.2, 137.8, 129.5, 127.8, 125.2, 124.6, 70.3, 67.7, 36.2; IR ν_{max} (neat)/cm^{-1}: 2104 (s), 1743(w), 1478 (w), 1247 (s).

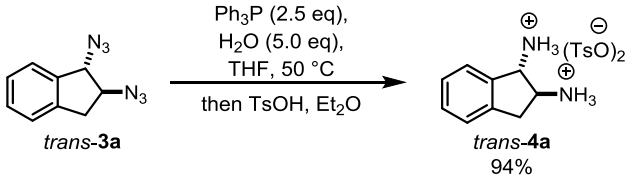
Note: it was challenging to obtain HRMS analysis of indene diazides **3a** and most of other diazides through ESI analysis; therefore, the HRMS analysis was performed with the corresponding diaminium salts after derivatization. Additionally, diazides **3d** and **3f** were both derived to bistriazole compounds through the click-reaction with phenylacetylene to confirm the structure (*vide infra*).



cis-**3a**

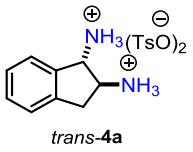
***cis*-1,2-Diazido-2,3-dihydro-1*H*-indene** (*cis*-**3a**): The minor diastereomer *cis*-**3a** is also a known compound: both the ^{1}H NMR and ^{13}C NMR data are in accordance with the literature data.[73]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45–7.27 (m, 4H), 4.84 (d, J = 5.6 Hz, 1H), 4.29 (dd, J = 12.3, 6.5 Hz, 1H), 3.25–3.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.8, 137.6, 129.8, 127.8, 125.5, 125.0, 67.1, 64.2, 35.7; IR ν_{max} (neat)/cm^{-1}: 2096 (s), 1742 (w), 1322 (m), 1242 (s).



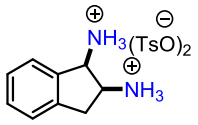
Scheme 64. Staudinger Reduction of Azides

The indene diazides **3a** (*trans*- and *cis*-) were both converted to diaminium salts **4a** through a 2-step procedure. To a 3-dram vial equipped with a stir bar were added *trans*-/*cis*-**3a** (60.0 mg, 0.3 mmol), THF (3 mL) and H_2O (27 μL, 1.5 mmol). After the vial was evacuated and backfilled with N_2 three times, a solution of PPh_3 (196.8 mg, 0.75 mmol) in THF (1.5 mL) was added drop-wise at 0 °C. The mixture was warmed up to 50 °C and stirred for 5 h (the reaction was monitored by IR until the absorption of azido groups disappeared). The mixture was then concentrated *in vacuo* and the residue was further dissolved in Et_2O (5 mL). This solution was added drop-wise to a solution of $TsOH{\cdot}H_2O$ (142.7 mg, 0.75 mmol) in Et_2O (3 mL). The reaction was kept stirring for 30 min and the white precipitate was collected by filtration, washed with Et_2O (5 mL × 3) and dried *in vacuo*.



(±)-(1*R*,2*R*)-2,3-Dihydro-1*H*-indene-1,2-diaminium ditosylate (*trans*-**4a**). *trans*-**4a** was prepared through the aforementioned reduction/protonation procedure and it was isolated as a white solid (94% yield, m.p. 276–279 °C). IR ν_{max} (neat)/cm^{-1}: 3036 (s), 2920 (s), 1599 (m), 1437 (w), 1166 (s), 1119 (s), 1032 (s), 1009 (s), 812 (m), 723 (m), 679 (s); ^{1}H NMR (400 MHz,

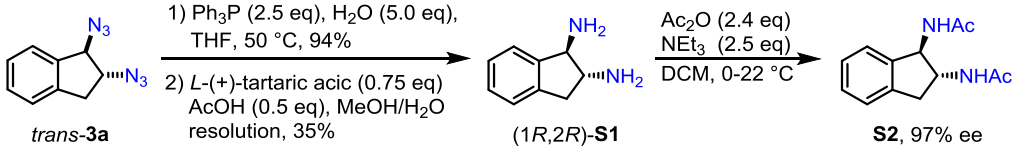
DMSO-*d*6): δ 8.37 (brs, 6H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 4H), 7.45–7.34 (m, 3H), 7.12 (d, *J* = 7.9 Hz, 4H), 4.82 (d, *J* = 4.9 Hz, 1H), 3.99 (dd, *J* = 13.7, 5.6 Hz, 1H), 3.47 (dd, *J* = 16.8, 8.3 Hz, 1H), 3.01 (dd, *J* = 16.8, 5.9 Hz, 1H), 2.29 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 144.9, 140.1, 138.3, 136.0, 130.0, 128.3, 127.8, 125.6, 125.2, 125.0, 58.5, 54.4, 35.5, 20.9; HRMS (ESI, m/z): calcd for $C_9H_{13}N_2^+$, [M + H^+], 149.1073, found 149.1067.



cis-**4a**

(±)-(1*R*,2*S*)-2,3-Dihydro-1*H*-indene-1,2-diaminium ditosylate (*cis*-**4a**). *cis*-**4a** was prepared through the aforementioned reduction/protonation procedure and it was isolated as a white solid (94% yield, m.p. 268–270 ˚C). IR ν_{max} (neat)/cm^{-1}: 2870 (s), 1634 (w), 1547 (w), 1218 (s), 1187 (s), 1153 (m), 1125 (s), 1038 (s), 1012 (s), 817 (m), 682 (s); ^{1}H NMR (400 MHz, DMSO-*d*6): δ 8.47 (brs, 6H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 4H), 7.43–7.32 (m, 3H), 7.15 (d, *J* = 7.8 Hz, 4H), 4.85 (d, *J* = 6.1 Hz, 1H), 4.18 (dd, *J* = 13.7, 7.1 Hz, 1H), 3.24 (ddd, *J* = 31.5, 16.0, 7.5 Hz, 2H), 2.30 (s, 6H); ^{13}C NMR (100 MHz, DMSO-*d*6): δ 144.6, 140.1, 138.5, 136.0, 130.2, 128.4, 127.7, 125.9, 125.6, 125.4, 54.9, 52.0, 34.1, 20.9; HRMS (ESI, m/z): calcd for $C_9H_{13}N_2^+$, [M + H^+], 149.1073, found 149.1067.

4.2.2.3 Optical Resolution of the Indene-(trans)-1,2-Diamine

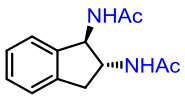


trans-**3a** (1*R*,2*R*)-**S1** **S2**, 97% ee

Scheme 65. Optical Resolution of the Indene-(trans)-1,2-Diamine

To a 3-dram vial equipped with a stir bar were added *trans*-**3a** (2.6 g, 13.0 mmol), THF (40 mL) and H_2O (1.2 mL, 65.0 mmol). After the vial was evacuated and backfilled with N_2 three

times, a solution of PPh_3 (8.18 g, 31.2 mmol) in THF (20 mL) was added drop-wise at 0 °C. The mixture was warmed up to 50 °C and stirred for 4 h (the reaction was monitored by IR until the absorption of azido groups disappeared). *L*-(+)-tartaric acid (1.47 g, 9.8 mmol) was dissolved in MeOH (5 mL) and added to the reaction mixture drop-wise at 50 °C. The White precipitate was formed and the whole mixture was kept stirring for another 10 min. Then AcOH (0.37 mL, 6.5 mmol) was added via a syringe. After refluxing for 2 min, the reaction was cooled down to room temperature without stirring. The resulting white precipitate was collected by filtration, washed with MeOH (5 mL × 2), EtOAc (10 mL × 2) and dried *in vacuo*. The white solid was dissolved in hot water (10 mL), and hot MeOH (11 mL) was added subsequently. The resulting solution was cooled down to room temperature and crystalline white solids precipitated out in 12 h. The solids were collected (1.09 g) by filtration and washed with a mixture of MeOH/H_2O (2:1, 5 mL), and then MeOH (5 mL). Another portion of white solids (220 mg) precipitated out of the filtrate, and they were also collected by filtration and dried *in vacuo*. Both solids were dissolved in NaOH solution (1 M), extracted with CH_2Cl_2 for four times and dried over anhydrous K_2CO_3 separately. Evaporation of the solvent afforded the chiral diamine **S1** as white solids (533 mg and 107 mg, 35% combined yield from diazide *trans*-**3a**). The *ee* of both solids was determined to be 97% by HPLC analysis after derivatization. Its configuration was determined as (1*R*,2*R*) by comparison of the optical rotation of the diamine **S1** ($[\alpha]_D^{20}$ = –20.3° (*c*=0.7 in $CHCl_3$)) with the one reported in literature ($[\alpha]_D^{25}$ = –20.4° (*c*=0.7 in $CHCl_3$)).[72]

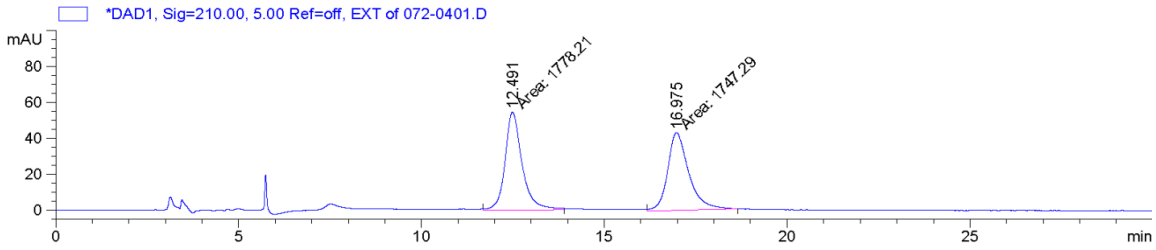


S2

***N,N'*-((1*R*,2*R*)-2,3-dihydro-1*H*-indene-1,2-diyl)diacetamide** (**S2**): Diamine **S1** (14.8 mg, 0.1 mmol) was dissolved in anhydrous CH_2Cl_2 (2 mL) in a flame-dried vial under N_2. The

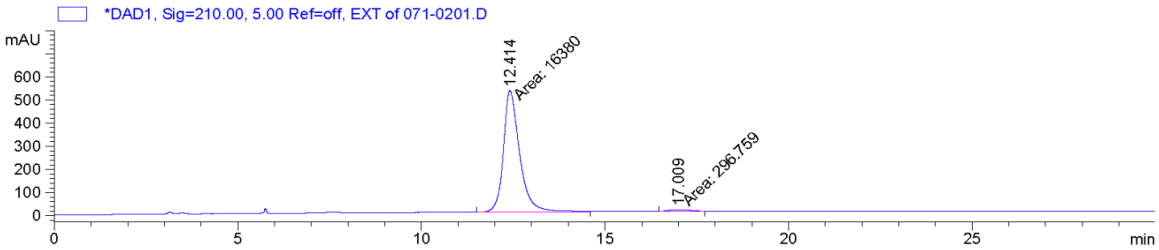
reaction was cooled to 0 °C and Et_3N (35 μL, 0.25 mmol) were added followed by dropwise addition of Ac_2O (23 μL, 0.24 mmol). The reaction was then warmed up to room temperature and kept stirring for 2 hours. After quenching with the saturated $NaHCO_3$ solution under vigorous stirring, the mixture was extracted with CH_2Cl_2 (2 mL × 3) and then concentrated *in vacuo*. The residue was purified through a silica gel flash column (hexanes/acetone from 2:1 to 1:2) to afford **S2** as a white solid (19.5 mg, 84% yield, m.p. decomposed at 250 ˚C). IR ν_{max} (neat)/cm^{-1}: 3271 (m), 3068 (w), 2937 (w), 1641 (s), 1542 (s), 1371 (m), 1295 (m); ^{1}H NMR (400 MHz, $CDCl_3$, 318 K): δ 7.25–7.08 (m, 4H), 6.74 (d, J = 5.5 Hz, 1H), 6.36 (d, J = 8.0 Hz, 1H), 5.34 (t, J = 8.7 Hz, 1H), 4.34–4.21 (m, 1H), 3.31 (dd, J = 15.5, 7.7 Hz, 1H), 2.63 (dd, J = 15.4, 9.8 Hz, 1H), 2.08 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 318 K): δ 171.5, 171.0, 139.9, 139.7, 128.3, 127.1, 124.9, 122.9, 59.8, 59.5, 36.8, 23.20, 23.15; HRMS (ESI, m/z): calcd for $C_{13}H_{17}N_2O_2^+$, [M + H^+], 233.1285, found 233.1283; $[\alpha]_D^{20}$ = –44.2 (c=1.0 in $CHCl_3$, 97% *ee*); The *ee* was determined by Chiral HPLC analysis (Chiral *S.S.* Whelk, 1.0 mL/min, 254 nm, 10% EtOH in hexanes, t_r (major) = 12.49 min, t_r (minor) = 16.98 min, 97% *ee*).

Racemic S2



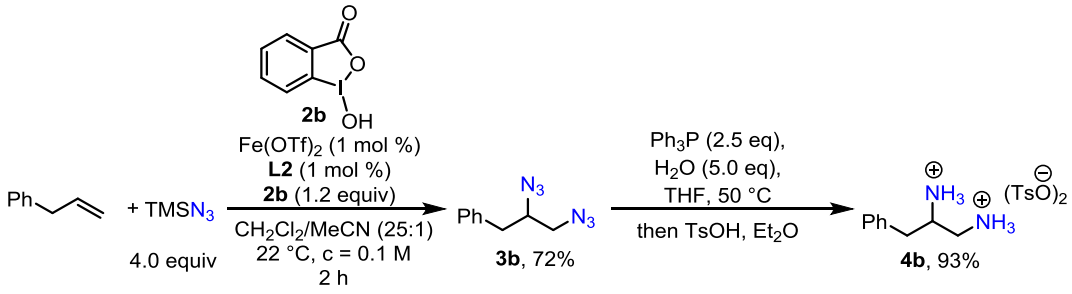
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.491	MM	0.5418	1778.21216	54.70387	50.4385
2	16.975	MM	0.6719	1747.29346	43.34398	49.5615
Totals :				3525.50562	98.04784	

Enantio-enriched S2 (97% *ee*)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.414	MM	0.5179	1.63800e4	527.09277	98.2205
2	17.009	MM	0.6612	296.75946	7.48080	1.7795
Totals :				1.66767e4	534.57357	

4.2.2.4 Procedure for the Iron-Catalyzed Olefin Diazidation and Product Characterization



Warning: Standard precautions with regard to handling $TMSN_3$ should be taken during the reaction workup since an extra equivalent of $TMSN_3$ is used when **2b** is directly used as the terminal oxidant.

For safely handling $TMSN_3$, see the MSDS sheet at:

http://www.sigmaaldrich.com/catalog/product/aldrich/155071.

Since the C/N ratios for these synthetically valuable diazides generally vary from 1 to 3, careful isolation and characterization of diazides was carried out under small-scale (<100 mg) conditions. Also, direct reduction of diazides to diamines without further concentration is carried out for most substrates.

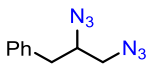
For safely handling organic azides, see:

https://web.stanford.edu/dept/EHS/prod/researchlab/lab/safety_sheets/08-203.pdf.

3.6 equiv. of $TMSN_3$ is sufficient for high yields with anhydrous **2b** that is stored in a glove-box. Alternatively, 4.0 equiv. of $TMSN_3$ is used to achieve the same yield with **2b** that is stored out of a glove-box.

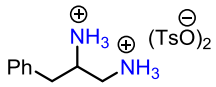
Allylbenzene is commercially available and was distilled before usage.

To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added $Fe(OTf)_2$ (1.8 mg, 0.005 mmol) and **L2** (1.4 mg, 0.005 mmol). After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (0.8 mL) and MeCN (0.2 mL) were added via a syringe and the mixture was stirred at room temperature for 10 min. To another flame-dried 3-dram vial (vial **B**) equipped with a stir bar was added **2b** (158.4 mg, 0.60 mmol). This vial was evacuated and backfilled with N_2 three times and anhydrous CH_2Cl_2 (4.0 mL) was added. Both vials were degassed with brief evacuation and backfilled with N_2 twice. Freshly distilled allylbenzene (66 μL, 0.5 mmol), $TMSN_3$ (263 μL, 2.0 mmol) were added successively to vial **B** and followed by drop-wise addition of the catalyst solution in vial **A** at room temperature. The reaction was kept at room temperature for 2 h and then quenched with a saturated $NaHCO_3$ solution (0.1 mL) and further diluted with hexanes (5 mL). The mixture was stirred vigorously for 10 min and filtered through a short silica gel pad. The filtrate was concentrated *in vacuo*. The residue was subsequently purified through a silica gel flash column (hexanes/Et_2O: from 200:1 to 50:1) as a colorless oil (72.8 mg, 72% yield).



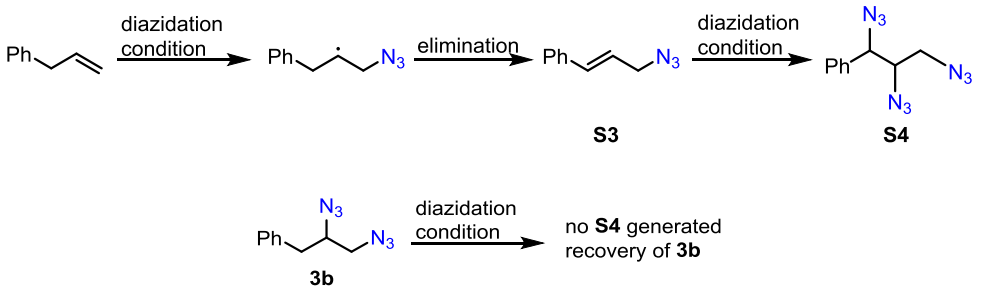
3b

(2,3-Diazidopropyl)benzene (**3b**): IR ν_{max} (neat)/cm^{-1}: 2932 (w), 2100 (s), 1205 (m), 743 (w); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.32 (m, 2H), 7.30–7.27 (m, 1H), 7.25–7.17 (m, 2H), 3.79–3.66 (m, 1H), 3.40 (dd, J = 12.7, 3.9 Hz, 1H), 3.29 (dd, J = 12.7, 6.9 Hz, 1H), 2.88 (d, J = 7.0 Hz, 2H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 136.5, 129.4, 129.0, 127.3, 63.0, 54.0, 38.1.

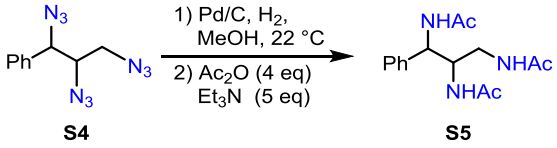


4b

3-Phenylpropane-1,2-diaminium ditosylate (**4b**). To a 3-dram vial equipped with a stir bar were added diazidation product **3b** (60.7 mg, 0.3 mmol), THF (3 mL) and H_2O (27 μL, 1.5 mmol). After the vial was evacuated and backfilled with N_2 three times, a solution of PPh_3 (196.8 mg, 0.75 mmol) in THF (1.5 mL) was added drop-wise at 0 °C. The mixture was warmed up to 50 °C and stirred for 6 h (the reaction was monitored by IR until the absorption of azido groups disappeared). The mixture was then concentrated *in vacuo* and the residue was further dissolved in Et_2O (5 mL). This solution was added drop-wise to a solution of $TsOH{\cdot}H_2O$ (142.7 mg, 0.75 mmol) in Et_2O (3 mL). The reaction was kept stirring for 30 min and the white precipitate was collected by filtration, washed with Et_2O (5 mL × 3) and dried *in vacuo*. **4b** was obtained as a white solid (138 mg, 93% yield, m.p. 217–219 ˚C). IR ν_{max} (neat)/cm^{-1}: 3059 (s), 2917 (m), 1496 (m), 1176 (s), 1120 (s), 1034 (m), 1010 (m), 812 (w), 723 (m), 679 (s); ^{1}H NMR (400 MHz, CD_3OD): δ 7.72 (d, J = 8.1 Hz, 4H), 7.40–7.27 (m, 5H), 7.24 (d, J = 7.9 Hz, 4H), 3.86 (m, 1H), 3.33 (dd, J = 13.9, 7.2 Hz, 1H), 3.23 (dd, J = 13.9, 5.4 Hz, 1H), 3.08 (dd, J = 14.2, 6.9 Hz, 1H), 2.99 (dd, J = 14.2, 6.9 Hz, 1H), 2.37 (s, 6H); ^{13}C NMR: (100 MHz, CD_3OD) δ 143.2, 142.0, 135.6, 130.5, 130.3, 130.0, 128.9, 126.9, 52.2, 42.0, 37.6, 21.3; HRMS (ESI, m/z): calcd for $C_9H_{15}N_2^+$, [M + H^+], 151.1230, found 151.1224.

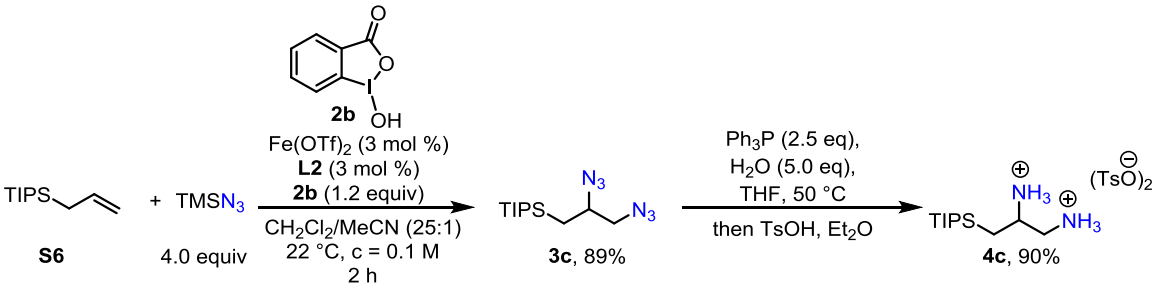


(1,2,3-Triazidopropyl)benzene (**S4**). A pair of tri-azidation products were isolated as side products as a colorless oil (17.0 mg, 14% yield, *dr* = 1.8:1). **S4** was generated presumably through the addition/elimination/addition sequence. Their structures were further corroborated through the analysis of the corresponding tri-amine. IR ν_{max} (neat)/cm^{-1}: 2922 (w), 2091 (s), 1454 (w), 1247 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50–7.30 (m, 5H), 4.63 (d, *J* = 8.0 Hz, 1H), 4.62 (d, *J* = 7.6 Hz, 1H, minor), 3.70 (ddd, *J* = 7.6, 6.9, 3.9 Hz, 1H, minor), 3.65 (ddd, *J* = 8.0, 6.5, 3.7 Hz, 1H), 3.54–3.44 (m, 2H, minor), 3.31 (dd, *J* = 12.8, 3.7 Hz, 1H), 3.09 (dd, *J* = 12.8, 6.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.4, 135.1 (minor), 129.5, 129.4 (minor), 129.4, 129.2 (minor), 127.8 (minor), 127.4, 67.3, 66.0 (minor), 65.7, 65.1 (minor), 51.8, 51.7 (minor).



***N*,*N*',*N*''-(1-Phenylpropane-1,2,3-triyl)triacetamide** (**S5**). The structure of **S4** was further confirmed after derivatization. To a 2-dram vial equipped with a stir bar was added Pd/C (1.5 mg, 10 wt%). After the vial was evacuated and backfilled twice with N_2, a solution of triazide **S4** (14.6 mg, 0.06 mmol, dissolved in 1 mL MeOH) was added. The mixture was degassed with brief evacuation and backfilled twice with N_2 and then three times with H_2. The reaction was vigorously stirred under H_2 at room temperature until the reduction completed (the reaction was monitored by IR until the absorption of azido groups disappeared). The solution

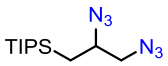
was filtered through Celite, washed with MeOH (3 mL) and the filtrate was concentrated *in vacuo*. Subsequently, the residue was dissolved in CH_2Cl_2 (2 mL) and cooled to 0 °C. Et_3N (42 μL, 0.3 mmol) was then added followed by dropwise addition of Ac_2O (23 μL, 0.24 mmol). The reaction was warmed up to room temperature and stirred for additional 4 h and quenched with a saturated $NaHCO_3$ solution (1 mL). After the organic layer was separated, the aqueous phase was extracted with CH_2Cl_2 (2 mL × 6). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified through a silica gel flash column (CH_2Cl_2/MeOH: from 20:1 to 5:1) to afford **S5** as a colorless oil (*dr* = 6:1). IR ν_{max} (neat)/cm^{-1}: 3281 (m), 3068 (w), 1641 (s), 1530 (s), 1371 (s), 1279 (m), 1118 (w); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.27 (m, 6H), 7.11 (d, *J* = 6.9 Hz, 1H), 6.68 (d, *J* = 7.2 Hz, 1H, minor), 6.34 (t, *J* = 5.3 Hz, 1H, minor), 6.01 (t, *J* = 5.3 Hz, 1H), 5.14 (dd, *J* = 7.9, 3.7 Hz, 1H, minor), 4.85 (dd, *J* = 10.3, 7.5 Hz, 1H), 4.42–4.34 (m, 1H, minor), 4.33–4.25 (m, 1H), 3.51–3.42 (m, 1H, minor), 3.38–3.29 (m, 1H, minor), 3.16 (t, *J* = 5.7 Hz, 2H), 2.07 (s, 3H, minor), 2.01 (s, 3H), 1.97 (s, 3H), 1.94 (s, 3H, minor), 1.93 (s, 3H), 1.85 (s, 3H, minor); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 172.9, 172.3, 170.5, 139.3, 129.2, 128.3, 127.2, 57.1, 55.5, 41.7, 23.4, 23.3, 23.1; HRMS (ESI, m/z): calcd for $C_{15}H_{20}N_3O_3^-$, [M - H^+], 290.1510, found 290.1501.



Allyl triisopropylsilane **S6** was prepared through a literature procedure.[74]

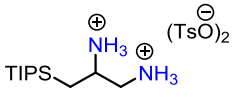
To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added $Fe(OTf)_2$ (5.3 mg, 0.015 mmol) and **L2** (4.1 mg, 0.015 mmol). After the vial was evacuated and

backfilled with N_2 three times, anhydrous CH_2Cl_2 (0.8 mL) and MeCN (0.2 mL) were added via a syringe and the mixture was stirred at room temperature for 10 min. To another flame-dried 3-dram vial (vial **B**) equipped with a stir bar was added **2b** (158.4 mg, 0.60 mmol). This vial was evacuated and backfilled with N_2 three times and anhydrous CH_2Cl_2 (4.0 mL) was added. Both vials were degassed with brief evacuation and backfilled with N_2 twice. Allyl triisopropylsilane **S6** (148 μL, 0.5 mmol), $TMSN_3$ (263 μL, 2.0 mmol) were added successively to vial **B** and followed by dropwise addition of the catalyst solution in vial **A** at room temperature. The reaction was kept at room temperature for 2 h and then quenched with a saturated $NaHCO_3$ solution (0.1 mL) and further diluted with hexanes (5 mL). The mixture was stirred vigorously for 10 min and filtered through a short silica gel pad. The filtrate was concentrated *in vacuo*. The residue was subsequently purified through a silica gel flash column (hexanes/Et_2O: from 200:1 to 50:1) as a colorless oil (125.7 mg, 89% yield).



3c

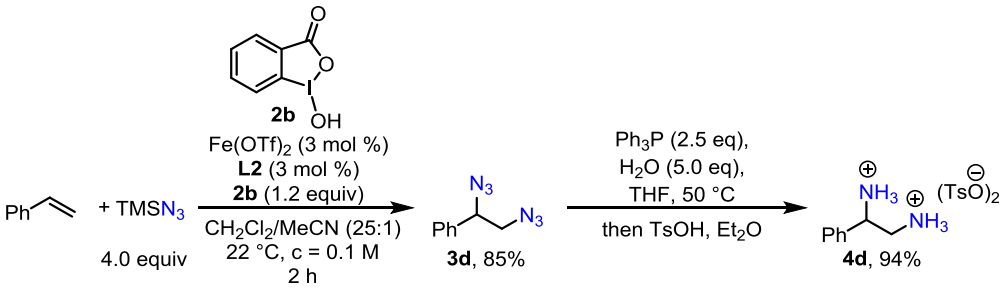
(2,3-Diazidopropyl)triisopropylsilane (**3c**): IR ν_{max} (neat)/cm^{-1}: 2942 (m), 2103 (s), 1463 (w), 1261 (m), 764 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 3.69–3.58 (m, 1H), 3.42 (dd, J = 12.5, 4.0 Hz, 1H), 3.35 (dd, J = 12.5, 7.6 Hz, 1H), 1.07 (s, 21H), 0.91 (dd, J = 15.0, 8.9 Hz, 1H), 0.84 (dd, J = 15.0, 5.6 Hz, 1H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 59.8, 58.0, 18.87, 18.84, 12.9, 11.4.



4c

3-(Triisopropylsilyl)propane-1,2-diaminium ditosylate (**4c**). To a 3-dram vial equipped with a stir bar were added diazidation product **3c** (84.8 mg, 0.3 mmol), THF (3 mL)

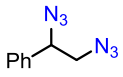
and H_2O (27 μL, 1.5 mmol). After the vial was evacuated and backfilled with N_2 three times, a solution of PPh_3 (196.8 mg, 0.75 mmol) in THF (1.5 mL) was added drop-wise at 0 °C. The mixture was warmed up to 50 °C and stirred for 6 h (the reaction was monitored by IR until the absorption of azido groups disappeared). The mixture was then concentrated *in vacuo* and the residue was further dissolved in Et_2O (5 mL). This solution was added drop-wise to another solution of $TsOH{\cdot}H_2O$ (142.7 mg, 0.75 mmol) in Et_2O (3 mL). The reaction was kept stirring for 30 min and the white precipitate was collected by filtration, washed with Et_2O (5 mL × 3) and dried *in vacuo*. **4c** was obtained as a white solid (155.2 mg, 90% yield, m.p. 246–248 ˚C). IR ν_{max} (neat)/cm^{-1}: 2942 (s), 1531 (m), 1171 (s), 1126 (s), 1035 (s), 1012 (s), 813 (m), 679(s); ^1H NMR (400 MHz, CD_3OD): δ 7.71 (d, J = 8.1 Hz, 4H), 7.24 (d, J = 8.0 Hz, 4H), 3.92–3.69 (m, 1H), 3.28 (d, J =14.3, 9.8 Hz, 1H), 3.21 (dd, J = 14.3, 3.0 Hz, 1H), 2.37 (s, 6H), 1.14 (d, J = 7.6 Hz, 2H), 1.08 (s, 21H); ^{13}C NMR (100 MHz, CD_3OD): δ 143.1, 142.0, 130.0, 126.9, 49.8, 44.2, 21.3, 19.18, 19.17, 14.4, 12.5; HRMS (ESI, m/z): calcd for $C_{12}H_{31}N_2Si^+$, [M + H^+], 231.2251, found 231.2247.



Styrene is commercially available and was distilled before usage.

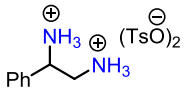
To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added $Fe(OTf)_2$ (5.3 mg, 0.015 mmol) and **L2** (4.1 mg, 0.015 mmol). After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (0.8 mL) and MeCN (0.2 mL) were added via a syringe and the mixture was stirred at room temperature for 10 min. To another flame-dried 3-

dram vial (vial **B**) equipped with a stir bar was added **2b** (158.4 mg, 0.60 mmol). This vial was evacuated and backfilled with N_2 three times and anhydrous CH_2Cl_2 (4.0 mL) was added. Both vials were degassed with brief evacuation and backfilled with N_2 twice. Freshly distilled styrene (57 μL, 0.5 mmol), $TMSN_3$ (263 μL, 2.0 mmol) were added successively to vial **B** and followed by drop-wise addition of the catalyst solution in vial **A** at room temperature. The reaction was kept at room temperature for 2 h and then quenched with saturated $NaHCO_3$ solution (0.1 mL) and further diluted with hexanes (5 mL). The mixture was stirred vigorously for 10 min and filtered through a short silica gel pad. The filtrate was concentrated *in vacuo*. The residue was subsequently purified through a silica gel flash column (hexanes/Et_2O: from 200:1 to 50:1) as colorless oil (80.0 mg, 85% yield).



3d

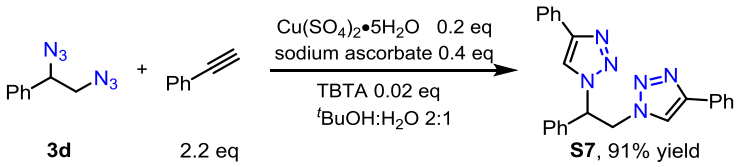
(1,2-Diazidoethyl)benzene (**3d**): IR ν_{max} (neat)/cm^{-1}: 2927 (w), 2099 (s), 1456 (w), 1152 (m); ^1H NMR (400 MHz, $CDCl_3$): δ 7.47–7.38 (m, 3H), 7.38–7.27 (m, 2H), 4.68 (dd, J = 8.2, 5.0 Hz, 1H), 3.51 (dd, J = 12.7, 8.3 Hz, 1H), 3.45 (dd, J = 12.7, 5.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.5, 129.2, 129.2, 127.1, 65.6, 56.1.



4d

1-Phenylethane-1,2-diaminium ditosylate (**4d**). To a 3-dram vial equipped with a stir bar were added diazidation product **3d** (56.5 mg, 0.3 mmol), THF (3 mL) and H_2O (27 μL, 1.5 mmol). After the vial was evacuated and backfilled with N_2 three times, a solution of PPh_3 (196.8 mg, 0.75 mmol) in THF (1.5 mL) was added drop-wise at 0 °C. The mixture was warmed up to 50 °C and stirred for 6 h (the reaction was monitored by IR until the absorption of azido groups

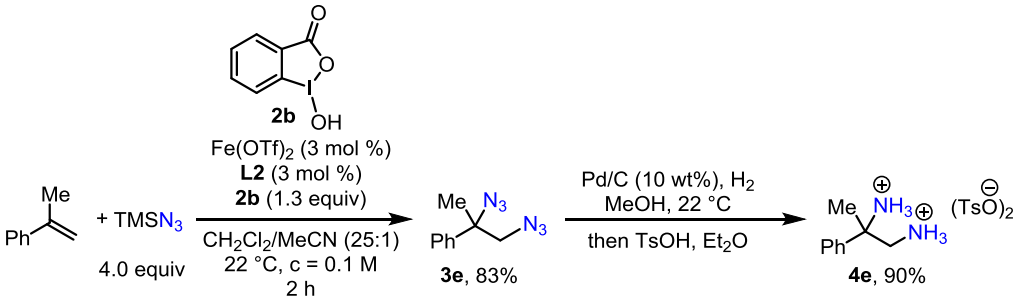
disappeared). The mixture was then concentrated *in vacuo* and the residue was further dissolved in Et_2O (5 mL). This solution was added drop-wise to another solution of $TsOH{\cdot}H_2O$ (142.7 mg, 0.75 mmol) in Et_2O (3 mL). The reaction was kept stirring for 30 min and the white precipitate was collected by filtration, washed with Et_2O (5 mL × 3) and dried *in vacuo*. **4d** was obtained as a white solid (126.9 mg, 88% yield, m.p. 245–247 ˚C). IR ν_{max} (neat)/cm^{-1}: 3053 (s), 2918 (s), 1620 (w), 1515 (m), 1193 (s), 1172 (s), 1126 (s), 1036 (s), 1011 (s), 812 (m), 759 (m), 697 (m), 680 (s); ^{1}H NMR (400 MHz, CD_3OD): δ 7.72 (d, J = 8.1 Hz, 4H), 7.59–7.54 (m, 2H), 7.54–7.48 (m, 3H), 7.25 (d, J = 8.0 Hz, 4H), 4.68 (dd, J = 9.4, 5.7 Hz, 1H), 3.66 (dd, J = 13.0, 5.7 Hz, 1H), 3.57 (dd, J = 13.0, 9.4 Hz, 1H), 2.38 (s, 6H); ^{13}C NMR (100 MHz, DMSO-*d*6): δ 144.8, 138.5, 133.8, 129.8, 129.2, 128.4, 128.1, 125.6, 52.2, 41.6, 20.9; HRMS (ESI, m/z): calcd for $C_8H_{13}N_2^+$, [M + H^+], 137.1073, found 137.1067.



3d 2.2 eq **S7**, 91% yield

1,1'-(1-Phenylethane-1,2-diyl)bis(4-phenyl-1H-1,2,3-triazole) (**S7**): Diazido compound **3d** (37.6 mg, 0.2 mmol) was dissolved in a 2:1 mixture of ^{t}BuOH and water (0.6 mL). Phenylacetylene (48 μL, 0.44 mmol), $CuSO_4{\cdot}5H_2O$ (10.0 mg, 0.04 mol), sodium ascorbate (15.9 mg, 0.08 mmol) and TBTA (tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine) (2.1 mg, 0.004 mmol) were added and the solution was stirred at room temperature for 1 h. The reaction mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (5 × 20 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was evaporated. The resulting solid was washed with ether (2 × 3 mL) and bistriazole **S7** was isolated as a white solid (71.4 mg, 91%). IR ν_{max} (neat)/cm^{-1}: 3091 (m), 1464 (s), 1231 (m), 1020 (m) 1081 (m), 1044 (w), 838 (w); ^{1}H NMR (400 MHz, DMSO-*d*6, 323K): δ 8.79 (s, 1H), 8.52 (s, 1H), 7.80 (d, J = 7.3 Hz, 2H), 7.75 (d, J = 7.4

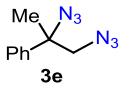
Hz, 2H), 7.58 (d, *J* = 7.0 Hz, 2H), 7.48 – 7.39 (m, 7H), 7.36 – 7.28 (m, 2H), 6.55 (dd, *J* = 9.7, 5.8 Hz, 1H), 5.62 (dd, *J* = 14.2, 9.9 Hz, 1H), 5.35 (dd, *J* = 14.2, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-*d*6, 323K): δ 147.0, 146.7, 136.6, 131.0, 130.9, 129.5, 129.33, 129.32, 128.5, 128.4, 127.8, 125.7, 125.6, 122.3, 121.5, 64.0, 52.7; HRMS (ESI, m/z): calcd for $C_{24}H_{20}N_6Na^+$, [M + Na^+], 415.1642, found 415.1636.



α-Methylstyrene is commercially available and was distilled before usage.

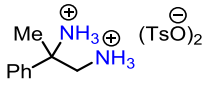
To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added $Fe(OTf)_2$ (5.3 mg, 0.015 mmol) and **L2** (4.1 mg, 0.015 mmol). After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (0.8 mL) and MeCN (0.2 mL) were added via a syringe and the mixture was stirred at room temperature for 10 min. To another flame-dried 3-dram vial (vial **B**) equipped with a stir bar was added **2b** (158.4 mg, 0.60 mmol). This vial was evacuated and backfilled with N_2 three times and anhydrous CH_2Cl_2 (4.0 mL) was added. Both vials were degassed with brief evacuation and backfilled with N_2 twice. Freshly distilled *α*-methylstyrene (65 μL, 0.5 mmol), $TMSN_3$ (263 μL, 2.0 mmol) were added successively to vial **B** and followed by drop-wise addition of the catalyst solution in vial **A** at room temperature. The reaction was kept at room temperature for 2 h and then quenched with a saturated $NaHCO_3$ solution (0.1 mL) and further diluted with hexanes (5 mL). The mixture was stirred vigorously for 10 min and filtered through a short silica gel pad. The filtrate was concentrated *in vacuo*. The

residue was subsequently purified through a silica gel flash column (hexanes/Et_2O: from 200:1 to 50:1) as a colorless oil (83.9 mg, 83% yield).



3e

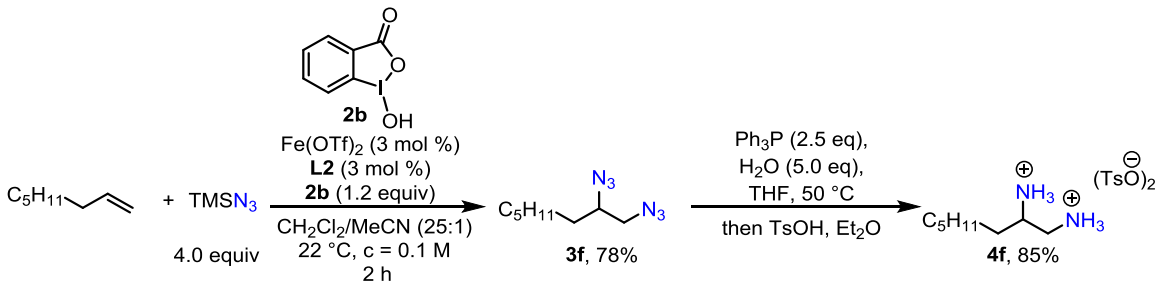
(1,2-Diazidopropan-2-yl)benzene (**3e**): IR ν_{max} (neat)/cm^{-1}: 2934 (m), 2097 (s), 1298 (m), 699 (m); ^1H NMR (400 MHz, $CDCl_3$): δ 7.46–7.40 (m, 4H), 7.38–7.31 (m, 1H), 3.50 (d, J = 12.6 Hz, 1H), 3.41 (d, J = 12.6 Hz, 1H), 1.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.7, 129.0, 128.4, 125.9, 66.7, 61.1, 22.4.



4e

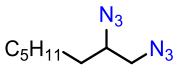
2-Phenylpropane-1,2-diaminium ditosylate (**4e**). To a 3-dram vial equipped with a stir the bar was added Pd/C (6.0 mg, 10 wt%). After the vial was evacuated and backfilled twice with N_2, a solution of diazidation product **3e** (60.7 mg, 0.3 mmol, dissolved in 3 mL MeOH) was added to the vial. The mixture was degassed with brief evacuation and backfilled twice with N_2 and then three times with H_2. The reaction was vigorously stirred under H_2 at room temperature until the reduction completed (the reaction was monitored by IR until the absorption of azido groups disappeared). The solution was filtered through Celite and washed with MeOH (3 mL). To the filtrate was added a solution of $TsOH{\cdot}H_2O$ (114.2 mg, 0.60 mmol) in methanol (3 mL). The mixture was concentrated *in vacuo* (to ca. 0.5 mL solvent left), then diluted with Et_2O (10 mL). The white precipitate was collected by filtration, washed with Et_2O (5 mL × 3) and dried *in vacuo*. **4e** was obtained as a white solid (133.5 mg, 90% yield, m.p. 187–188 ˚C). IR ν_{max} (neat)/cm^{-1}: 3307 (s), 2944 (m), 2832 (w), 1449 (w), 1415 (w), 1260 (w), 1022 (s), 765 (m), 750 (m); ^1H NMR (400 MHz, CD_3OD): δ 7.74 (d, J = 8.0 Hz, 4H), 7.67–7.61 (m, 2H), 7.61–7.50 (m, 3H), 7.27 (d, J = 8.0 Hz, 4H), 3.74 (d, J = 13.5 Hz, 1H), 3.64 (d, J = 13.5 Hz, 1H), 2.41 (s, 6H),

1.95 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 143.2, 141.9, 138.6, 130.7, 130.5, 129.9, 126.9, 126.8, 58.0, 48.7, 23.6, 21.3; HRMS (ESI, m/z): calcd for $C_9H_{15}N_2^+$, [M + H^+], 151.1230, found 151.1228.



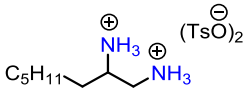
1-Octene is commercially available and was distilled before usage.

To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added $Fe(OTf)_2$ (5.3 mg, 0.015 mmol) and **L2** (4.1 mg, 0.015 mmol). After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (0.8 mL) and MeCN (0.2 mL) were added via a syringe and the mixture was stirred at room temperature for 10 min. To another flame-dried 3-dram vial (vial **B**) equipped with a stir bar was added **2b** (158.4 mg, 0.60 mmol). This vial was evacuated and backfilled with N_2 three times and anhydrous CH_2Cl_2 (4.0 mL) was added. Both vials were degassed with brief evacuation and backfilled with N_2 twice. Freshly distilled octene (79 μL, 0.5 mmol), $TMSN_3$ (263 μL, 2.0 mmol) were added successively to vial **B** and followed by drop-wise addition of the catalyst solution in vial **A** at room temperature. The reaction was kept at room temperature for 2 h and then quenched with saturated $NaHCO_3$ solution (0.1 mL) and further diluted with hexanes (5 mL). The mixture was stirred vigorously for 10 min and filtered through a short silica gel pad. The filtrate was concentrated *in vacuo*. The residue was subsequently purified through a silica gel flash column (hexanes/Et_2O: from 200:1 to 50:1) as colorless oil (76.5 mg, 78% yield).



3f

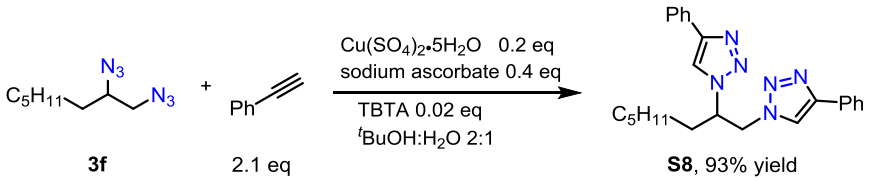
1,2-Diazidooctane (**3f**): IR ν_{max} (neat)/cm^{-1}: 2930 (m), 2099 (s), 1152 (s), 820 (w); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.50–3.41 (m, 1H), 3.38 (dd, J = 12.6, 3.8 Hz, 1H), 3.31 (dd, J = 12.6, 7.4 Hz, 1H), 1.59–1.50 (m, 2H), 1.50–1.41 (m, 1H), 1.41–1.20 (m, 7H), 0.89 (t, J = 5.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 62.2, 55.0, 31.9, 31.7, 29.1, 26.0, 22.7, 14.2.



4f

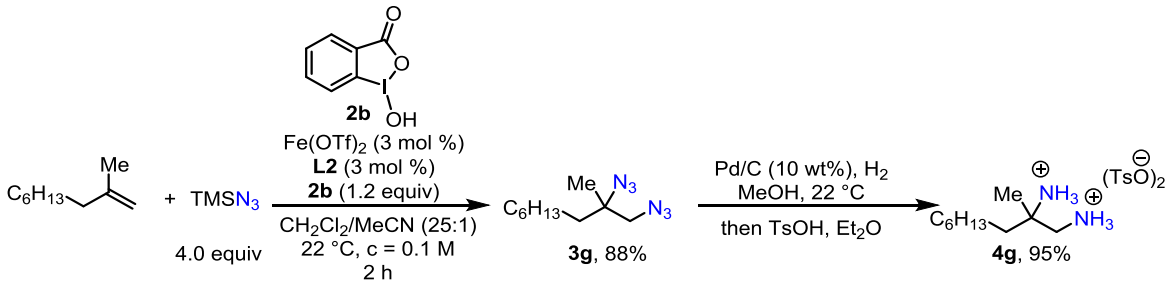
Octane-1,2-diaminium ditosylate (**4f**). To a 3-dram vial equipped with a stir bar were added diazidation product **3f** (58.9 mg, 0.3 mmol), THF (3 mL) and H_2O (27 μL, 1.5 mmol). After the vial was evacuated and backfilled with N_2 three times, a solution of PPh_3 (196.8 mg, 0.75 mmol) in THF (1.5 mL) was added drop-wise at 0 °C. The mixture was warmed up to 50 °C and stirred for 6 h (the reaction was monitored by IR until the absorption of azido groups disappeared). The mixture was then concentrated *in vacuo* and the residue was further dissolved in Et_2O (5 mL). This solution was added drop-wise to another solution of $TsOH{\cdot}H_2O$ (142.7 mg, 0.75 mmol) in Et_2O (3 mL). The reaction was kept stirring for 30 min and the white precipitate was collected by filtration, washed with Et_2O (5 mL × 3) and dried *in vacuo*. **4f** was obtained as a white solid (124.6 mg, 85% yield, m.p. 311–312 ˚C). IR ν_{max} (neat)/cm^{-1}: 2922 (s), 2857 (s), 1532 (w), 1168 (s), 1123 (s), 1035 (s), 1010 (s), 813 (m), 679 (s); ^{1}H NMR (400 MHz, CD_3OD): δ 7.71 (d, J = 8.1 Hz, 4H), 7.25 (d, J = 7.9 Hz, 4H), 3.53 (dt, J = 12.6, 6.2 Hz, 1H), 3.26 (dd, J = 12.5, 3.9 Hz, 1H), 3.22 (dd, J = 12.5, 5.2 Hz, 1H), 2.37 (s, 6H), 1.81–1.55 (m, 2H), 1.50–1.19 (m, 8H), 0.90 (t, J = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 154.3, 147.8, 137.8, 135.0,

58.5, 50.1, 40.5, 39.3, 37.9, 33.7, 31.5, 30.3, 23.5; HRMS (ESI, m/z): calcd for $C_8H_{21}N_2^+$, [M + H^+], 145.1699, found 145.1694.



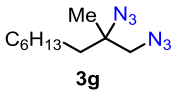
3f 2.1 eq **S8**, 93% yield

1,1'-(Octane-1,2-diyl)bis(4-phenyl-1H-1,2,3-triazole) (**S8**): Diazido compound **3f** (39.2 mg, 0.2 mmol) was dissolved in a 2:1 mixture of ^{t}BuOH and water (0.6 mL). Phenylacetylene (48 μL, 0.44 mmol), $CuSO_4 \cdot 5H_2O$ (10.0 mg, 0.04 mol), sodium ascorbate (15.9 mg, 0.08 mmol) and TBTA (tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine) (2.1 mg, 0.004 mmol) were added and the solution was stirred at room temperature for 2 h. The reaction mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was evaporated. The residue was then purified through a silica gel flash column (hexanes/acetone: from 10:1 to 3:1). Bistriazole **S8** was isolated as a white solid (74.4 mg, 93%). IR ν_{max} (neat)/cm^{-1}: 3083 (m), 2924 (m), 2857 (w), 1464 (m), 1226 (m), 1075 (w), 1044 (w); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77–7.69 (m, 2H), 7.69–7.61 (m, 2H), 7.49 (s, 1H), 7.41–7.26 (m, 6H), 7.30 (s, 1H), 5.04–4.88 (m, 3H), 2.31–2.15 (m, 1H), 2.11–1.98 (m, 1H), 1.40–1.20 (m, 8H), 0.86 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.9, 147.6, 130.0, 129.9, 128.8, 128.8, 128.4, 128.3, 125.74, 125.73, 120.72, 120.68, 62.2, 53.8, 32.7, 31.4, 28.7, 25.7, 22.5, 14.0; HRMS (ESI, m/z): calcd for calcd for $C_{24}H_{29}N_6^+$, [M + H^+], 401.2448, found 401.2450.



2-Methyl-1-nonene is commercially available and was distilled before usage.

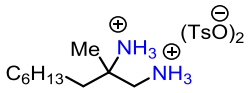
To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added $Fe(OTf)_2$ (5.3 mg, 0.015 mmol) and **L2** (4.1 mg, 0.015 mmol). After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (0.8 mL) and MeCN (0.2 mL) were added via a syringe and the mixture was stirred at room temperature for 10 min. To another flame-dried 3-dram vial (vial **B**) equipped with a stir bar was added **2b** (158.4 mg, 0.60 mmol). This vial was evacuated and backfilled with N_2 three times and anhydrous CH_2Cl_2 (4.0 mL) was added. Both vials were degassed with brief evacuation and backfilled with N_2 twice. Freshly distilled 2-methylnon-1-ene (94.1 μl, 0.5 mmol), $TMSN_3$ (263 μL, 2.0 mmol) were added successively to vial **B** and followed by drop-wise addition of the catalyst solution in vial **A** at room temperature. The reaction was kept at room temperature for 2 h and then quenched with a saturated $NaHCO_3$ solution (0.1 mL) and further diluted with hexanes (5 mL). The mixture was stirred vigorously for 10 min and filtered through a short silica gel pad. The filtrate was concentrated *in vacuo*. The residue was subsequently purified through a silica gel flash column (hexanes/Et_2O: from 200:1 to 50:1) as a colorless oil (98.7 mg, 88% yield).



3g

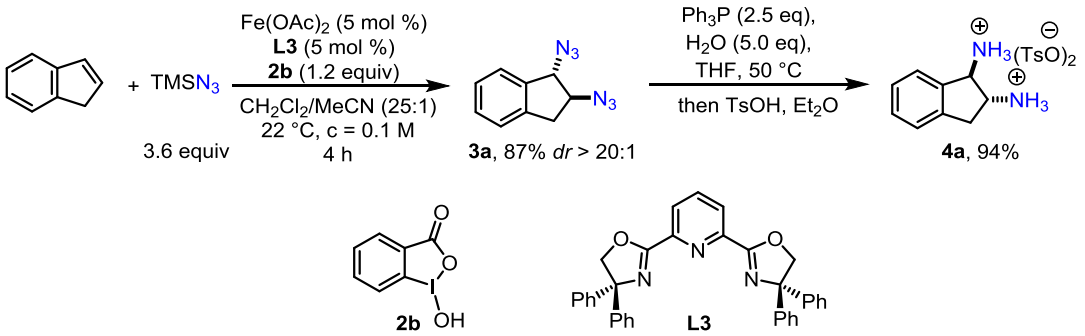
1,2-Diazido-2-methylnonane (**3g**): IR ν_{max} (neat)/cm^{-1}: 2929 (s), 2857 (w), 2094 (s), 1603 (m), 1460 (m), 1256 (s), 1152 (s), 1069 (w); ^1H NMR (400 MHz, $CDCl_3$): δ 3.28 (d, J =

12.4 Hz, 1H), 3.23 (d, *J* = 12.5 Hz, 1H), 1.54 (m, 2H), 1.30 (m, 13H), 0.89 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 64.0, 59.2, 37.5, 31.9, 29.9, 29.3, 23.8, 22.8, 21.4, 14.2.



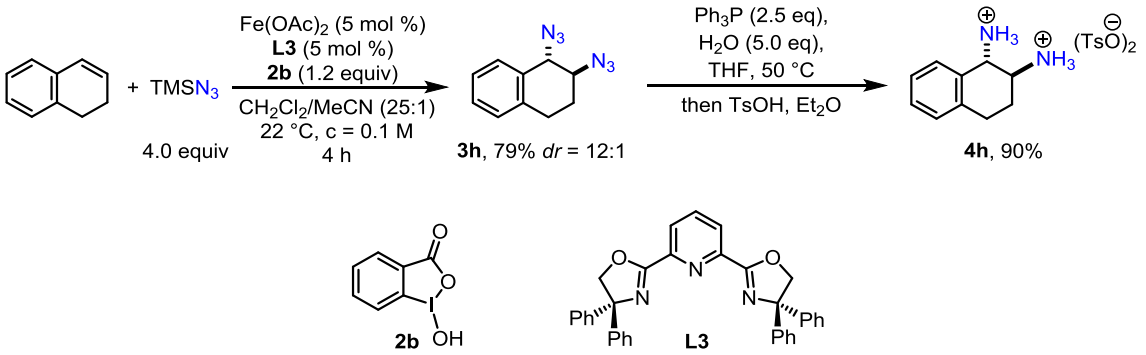
4g

2-Methylnonane-1,2-diaminium ditosylate (**4g**). To a 3-dram vial equipped with a stir bar was added Pd/C (6.7 mg, 10 wt%). After the vial was evacuated and backfilled twice with N_2, a solution of diazidation product **3g** (67.3 mg, 0.3 mmol, dissolved in 3 mL MeOH) was added to the vial. The mixture was degassed with brief evacuation and backfilled twice with N_2 and then three times with H_2. The reaction was vigorously stirred under H_2 at room temperature until the reduction completed (the reaction was monitored by IR until the absorption of azido groups disappeared). The solution was filtered through Celite and washed with MeOH (3 mL). To the filtrate was added a solution of $TsOH{\cdot}H_2O$ (114.2 mg, 0.60 mmol) in methanol (3 mL). The mixture was concentrated *in vacuo* (to ca. 0.5 mL solvent left), then diluted with Et_2O (10 mL). The white precipitate was collected by filtration, washed with Et_2O (5 mL × 3) and dried *in vacuo*. **4g** was obtained as a white solid (147.3 mg, 95% yield, m.p. 236–237 ˚C). IR ν_{max} (neat)/cm^{-1}: 2921 (s), 2854 (s), 2271 (w), 1531 (w), 1190 (s), 1125 (s), 1036 (s), 1012 (s), 816 (m), 679 (s); ^{1}H NMR (400 MHz, CD_3OD): δ 7.72 (d, *J* = 8.1 Hz, 4H), 7.24 (d, *J* = 7.9 Hz, 4H), 3.28 (d, *J* = 13.8 Hz, 1H), 3.24 (d, *J* = 13.8 Hz, 1H), 2.37 (s, 6H), 1.71 (m, 2H), 1.43 (s, 3H), 1.40–1.20 (m, 10H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 143.1, 142.0, 130.0, 126.9, 56.3, 46.4, 37.2, 32.9, 30.6, 30.1, 23.7, 23.6, 21.5, 21.3, 14.4; HRMS (ESI, m/z): calcd for $C_{10}H_{25}N_2^+$, [M + H$^+$], 173.2012, found 173.2010.



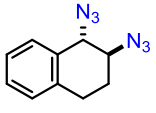
Indene is commercially available and was distilled before usage.

To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stirring bar were added $Fe(OAc)_2$ (4.4 mg, 0.025 mmol) and **L3** (13.1 mg, 0.025 mmol). After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (0.8 mL) and MeCN (0.2 mL) were added via a syringe and the mixture was stirred at room temperature for 10 min. To another flame-dried 3-dram vial (vial **B**) equipped with a stirring bar was added **2b** (158.4 mg, 0.60 mmol). This vial was evacuated and backfilled with N_2 three times and anhydrous CH_2Cl_2 (4.0 mL) was added. Both vials were degassed with brief evacuation and backfilled with N_2 twice. Freshly distilled indene (58 μl, 0.5 mmol), $TMSN_3$ (237 μl, 1.8 mmol) were added successively to vial **B** and followed by drop-wise addition of the catalyst solution in vial **A** at room temperature. The reaction was kept at room temperature for 4 h and then quenched with a saturated $NaHCO_3$ solution (0.1 mL) and further diluted with hexanes (5 mL). The mixture was stirred vigorously for additional 10 min and filtered through a short silica gel pad. The filtrate was concentrated *in vacuo*. The residue was subsequently purified through a silica gel flash column (hexanes/Et_2O: from 200:1 to 10:1) as a colorless oil (87.1 mg, 87 % yield, *dr* > 20:1).



1,2-Dihydronaphthalene is commercially available and was distilled before usage.

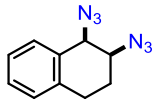
To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stirring bar were added $Fe(OAc)_2$ (4.4 mg, 0.025 mmol) and **L3** (13.1 mg, 0.025 mmol). After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (0.8 mL) and MeCN (0.2 mL) were added via a syringe and the mixture was stirred at room temperature for 10 min. To another flame-dried 3-dram vial (vial **B**) equipped with a stirring bar was added **2b** (158.4 mg, 0.60 mmol). This vial was evacuated and backfilled with N_2 three times and anhydrous CH_2Cl_2 (4.0 mL) was added. Both vials were degassed with brief evacuation and backfilled with N_2 twice. Freshly distilled 1,2-dihydronaphthalene (65 µl, 0.5 mmol), $TMSN_3$ (263 µl, 2.0 mmol) were added successively to vial **B** and followed by drop-wise addition of the catalyst solution in vial **A** at room temperature. The reaction was kept at room temperature for 4 h and then quenched with saturated $NaHCO_3$ solution (0.1 mL) and further diluted with hexanes (5 mL). The mixture was stirred vigorously for additional 10 min and filtered through a short silica gel pad. The filtrate was concentrated *in vacuo*. The residue was subsequently purified through a silica gel flash column (hexanes/Et_2O: from 200:1 to 10:1) as colorless oil (84.6 mg, 79 % yield, *dr* = 12:1).



trans-**3h**

***trans*-1,2-Diazido-1,2,3,4-tetrahydronaphthalene** (*trans*-**3h**): IR ν_{max} (neat)/cm^{-1}: 2927

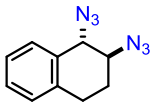
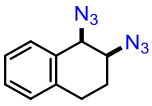
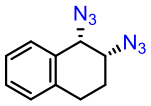
(w), 2094 (s), 1256(m), 748 (w); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, J = 3.4 Hz, 1H), 7.31–7.22 (m, 2H), 7.15 (d, J = 3.0 Hz, 1H), 4.43 (d, J = 6.6 Hz, 1H), 3.87 (ddd, J = 8.9, 6.6, 3.1 Hz, 1H), 3.00–2.82 (m, 2H), 2.29–2.19 (m, 1H), 2.04–1.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.8, 131.7, 129.15, 129.13, 128.7, 126.9, 63.6, 61.7, 26.1, 25.3.

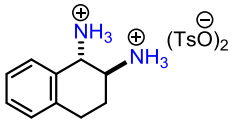


cis-**3h**

***cis*-1,2-Diazido-1,2,3,4-tetrahydronaphthalene** (*cis*-**3h**): IR ν_{max} (neat)/cm^{-1}: 2937 (w), 2095 (s), 1252(m), 767 (w); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.28 (m, 1H), 7.28–7.23 (m, 2H), 7.19 (d, J = 7.3 Hz, 1H), 4.65 (d, J = 3.2 Hz, 1H), 3.81 (dt, J = 11.4, 3.4 Hz, 1H), 3.07 (ddd, J = 17.4, 6.1, 3.4 Hz, 1H), 2.90 (ddd, J = 17.4, 10.6, 6.6 Hz, 1H), 2.30–2.15 (m, 1H), 2.15–2.02 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.5, 131.8, 129.8, 129.5, 129.3, 126.7, 62.7, 59.9, 27.5, 23.0.

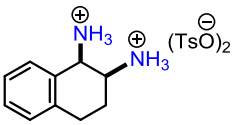
The relative stereochemistry was determined by comparison of ^{1}H NMR with literature data.[75]

	 *trans*-**3h**	 *cis*-**3h**	 (*1S,2R*)[5]
^{1}H NMR	^{1}H NMR (400 MHz, $CDCl_3$): δ 4.43 (d, J = 6.6 Hz, 1H), 3.87 (ddd, J = 8.9, 6.6, 3.1 Hz, 1H), 3.00–2.82 (m, 2H), 2.29–2.19 (m, 1H), 2.04–1.91 (m, 1H).	^{1}H NMR (400 MHz, $CDCl_3$): δ 4.65 (d, J = 3.2 Hz, 1H), 3.81 (dt, J = 11.4, 3.4 Hz, 1H), 3.07 (ddd, J = 17.4, 6.1, 3.4 Hz, 1H), 2.90 (ddd, J = 17.4, 10.6, 6.6 Hz, 1H), 2.30–2.15 (m, 1H), 2.15–2.02 (m, 1H).	^{1}H NMR (300MHz, $CDCl_3$): δ 4.65 (d, J = 2.3 Hz, 1H); 3.80 (ddd, J = 10.4, 4.6, 2.3 Hz, 1H), 3.09 (ddd, J = 16.1, 4.0, 5.8 Hz, 1H), 2.88 (ddd, J = 16.1, 10.4, 5.8 Hz, 1H), 2.18 (m, 2H).



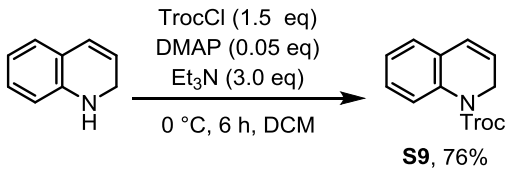
trans-**4h**

(±)-(1*S*,2*S*)-1,2,3,4-Tetrahydronaphthalene-1,2-diaminium ditosylate (*trans*-**4h**). To a 3-dram vial equipped with a stir bar were added *trans*-diazidation product *trans*-**3h** (64.3 mg, 0.3 mmol), THF (3 mL) and H_2O (27 μL, 1.5 mmol). After the vial was evacuated and backfilled with N_2 three times, a solution of PPh_3 (196.8 mg, 0.75 mmol) in THF (1.5 mL) was added drop-wise at 0 °C. The mixture was warmed up to 50 °C and stirred for 6 h (the reaction was monitored by IR until the absorption of azido groups disappeared). The mixture was then concentrated *in vacuo* and the residue was further dissolved in Et_2O (5 mL). This solution was added drop-wise to another solution of $TsOH{\cdot}H_2O$ (142.7 mg, 0.75 mmol) in Et_2O (3 mL). The reaction was kept stirring for 30 min and the white precipitate was collected by filtration, washed with Et_2O (5 mL × 3) and dried *in vacuo*. *trans*-**4h** was obtained as a white solid (136.7 mg, 86 % yield, decomposed at 280 ˚C). IR ν_{max} (neat)/cm^{-1}: 3026 (s), 2919 (s), 1610 (m), 1497 (w), 1163 (s), 1125 (s), 1036 (s), 1011 (s), 814 (m), 685 (s); ^{1}H NMR (400 MHz, CD_3OD): δ 7.70 (d, J = 8.1 Hz, 4H), 7.48 (d, J = 7.6 Hz, 1H), 7.42 (t, J = 7.1 Hz, 1H), 7.38–7.28 (m, 2H), 7.24 (d, J = 7.9, 4H), 4.69 (d, J = 3.1 Hz, 1H), 4.07–3.95 (m, 1H), 3.04 (dt, J = 18.0, 5.5 Hz, 1H), 2.99–2.88 (m, 1H), 2.37 (s, 6H), 2.35–2.27 (m, 1H), 2.20–2.09 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 144.9, 138.3, 136.6, 129.9, 129.4, 129.3, 128.8, 128.4, 127.0, 125.6, 50.0, 48.5, 23.9, 22.2, 20.9; HRMS (ESI, m/z): calcd for $C_{10}H_{15}N_2^+$, [M + H^+], 163.1230, found 163.1223.



cis-**4h**

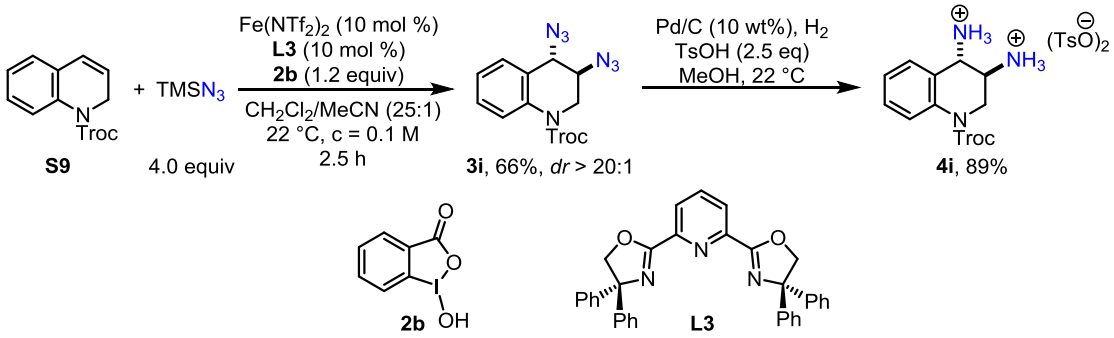
(±)-(1*R*,2*S*)-1,2,3,4-Tetrahydronaphthalene-1,2-diaminium ditosylate (*cis*-**4h**). To a 2-dram vial equipped with a stir bar was added Pd/C (2.1 mg, 10 wt%). After the vial was evacuated and backfilled twice with N_2, a solution of diazidation product *cis*-**3h** (21.4 mg, 0.1 mmol, dissolved in 1.5 mL MeOH) was added to the vial. The mixture was degassed with brief evacuation and backfilled twice with N_2 and then three times with H_2. The reaction was vigorously stirred under H_2 at room temperature until the reduction completed (the reaction was monitored by IR until the absorption of azido groups disappeared). The solution was filtered through Celite and washed with MeOH (3 mL). To the filtrate was added a solution of $TsOH{\cdot}H_2O$ (114.2 mg, 0.60 mmol) in methanol (3 mL). The mixture was concentrated *in vacuo* (to ca. 0.5 mL solvent left), then diluted with Et_2O (10 mL). The white precipitate was collected by filtration, washed with Et_2O (5 mL × 3) and dried *in vacuo*. *cis*-**4h** was obtained as a white solid (46.0 mg, 90% yield, decomposed at 280 ˚C). IR ν_{max} (neat)/cm^{-1}: 3401 (s), 1652 (m), 1048 (w), 994 (s), 824 (m), 762 (w); ^{1}H NMR (400 MHz, DMSO-*d*6): δ 8.32 (brs, 6H), 7.51 (d, J = 7.9 Hz, 4H), 7.44–7.33 (m, 2H), 7.31–7.21 (m, 2H), 7.14 (d, J = 7.8 Hz, 4H), 4.61 (d, J = 2.3 Hz, 1H), 3.79 (d, J = 12.4 Hz, 1H), 3.07–2.83 (m, 2H), 2.29 (s, 6H), 2.22–2.09 (m, 1H), 2.08–1.98 (m, 1H); ^{13}C NMR (100 MHz, DMSO-*d*6): δ 145.0, 138.2, 136.0, 130.3, 129.9, 129.7, 129.3, 128.3, 126.4, 125.6, 50.0, 48.7, 26.8, 20.9, 20.7; HRMS (ESI, m/z): calcd for $C_{10}H_{15}N_2$ [M + H^+], 163.1230, found 163.1223.



S9, 76%

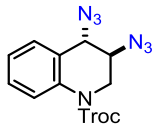
2,2,2-Trichloroethyl quinoline-1(2*H*)-carboxylate (**S9**). To a solution of 3,4-dihydroquinoline (234.4 mg, 2.0 mmol) in CH_2Cl_2 (10 mL) cooled in an ice-water bath, Et_3N (831 µL, 6.0 mmol) and DMAP (12.2 mg, 0.1 mmol) were added, followed by drop-wise

addition of 2,2,2-trichlorethoxycarbonyl chloride (0.41 mL, 3.0 mmol). The reaction was kept stirring in an ice-water bath for 6 h until starting material was consumed. Then the reaction mixture was diluted with water (50 mL) and extracted with CH_2Cl_2 (25 mL × 3). The combined organic layer was washed with brine (25 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified through a silica gel flash column (hexanes/EtOAc = 10:1) to afford **S9** as a white solid (466.0 mg, 76% yield). IR ν_{max} (neat)/cm^{-1}: 3049 (w), 2850 (w), 1715 (s), 1940 (m), 1387 (s), 1334 (m), 1223 (s), 1130 (s), 754 (m); ^1H NMR (400 MHz, CD_3CN): δ 7.67 (d, J = 8.1 Hz, 1H), 7.29–7.21 (m, 1H), 7.18–7.12 (m, 2H), 6.58 (d, J = 9.6 Hz, 1H), 6.14–6.06 (m, 1H), 4.90 (s, 2H), 4.45 (dd, J = 4.1, 1.6 Hz, 2H); ^{13}C NMR (100 MHz, CD_3CN): δ 152.2, 135.6, 128.3, 127.4, 126.4, 126.0, 125.1, 123.9, 117.3, 95.4, 75.1, 43.6; HRMS (ESI, m/z): calcd for $C_{12}H_{11}Cl_3NO_2^+$, [M + H^+], 305.9850, found 305.9860.



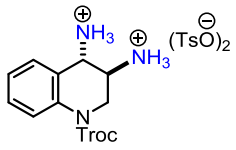
To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stirring bar were added $Fe(NTf_2)_2$ (30.8 mg, 0.05 mmol) and **L3** (26.1 mg, 0.05 mmol). After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (0.8 mL) and MeCN (0.2 mL) were added via a syringe and the mixture was stirred at room temperature for 10 min. To another flame-dried 3-dram vial (vial **B**) equipped with a stirring bar were added **2b** (158.4 mg, 0.60 mmol) and **S9** (153.3 mg, 0.5 mmol). This vial was evacuated and backfilled with N_2 three times and anhydrous CH_2Cl_2 (4.0 mL) was added. Both vials were degassed with brief evacuation and backfilled with

N_2 twice. $TMSN_3$ (263 μl, 2.0 mmol) was added to vial **B** and followed by drop-wise addition of the catalyst solution in vial **A** at room temperature. The reaction was kept at room temperature for 2.5 h and then quenched with saturated $NaHCO_3$ solution (0.1 mL), and further diluted with hexanes (5 mL). The mixture was stirred vigorously for 10 min and filtered through a short silica gel pad. The filtrate was concentrated *in vacuo*. The residue was subsequently purified through a silica gel flash column (hexanes/Et_2O: from 200:1 to17:1) as colorless oil (128.9 mg, 66% yield, *dr* > 20:1).



3i

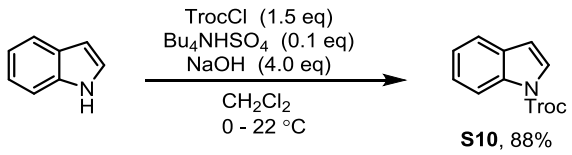
2,2,2-Trichloroethyl-*trans*-3,4-diazido-3,4-dihydroquinoline-1(2*H*)-carboxylate (**3i**): The relative stereochemistry was determined by comparison of its ^1H NMR spectra with the one obtained from **3h**. IR ν_{max} (neat)/cm^{-1}: 2956 (w), 2098 (s), 1722 (s), 1492 (s), 1391 (m), 1206 (m), 1146 (m), 760 (m); ^1H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, J = 6.9 Hz, 1H), 7.45–7.33 (m, 2H), 7.26–7.19 (m, 1H), 4.89 (s, 2H), 4.51 (d, J = 4.9 Hz, 1H), 4.15 (dd, J = 13.5, 5.8, 1H), 4.06–3.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7, 136.5, 129.5, 129.3, 125.3, 124.1, 123.6, 95.1, 75.7, 61.0, 59.2, 45.2; HRMS (ESI, m/z): calcd for $C_{12}H_{10}Cl_3N_7O_2Na^+$, [M + Na^+], 418.9854, found 418.9854.



4i

(±)-(3*S*,4*S*)-1-((2,2,2-Trichloroethoxy)carbonyl)-1,2,3,4-tetrahydroquinoline-3,4-diaminium ditosylate (**4i**). To a 3-dram vial equipped with a stir bar were added Pd/C (11.7 mg, 10 wt%) and $TsOH{\cdot}H_2O$ (142.7 mg, 0.75 mmol). After the vial was evacuated and backfilled

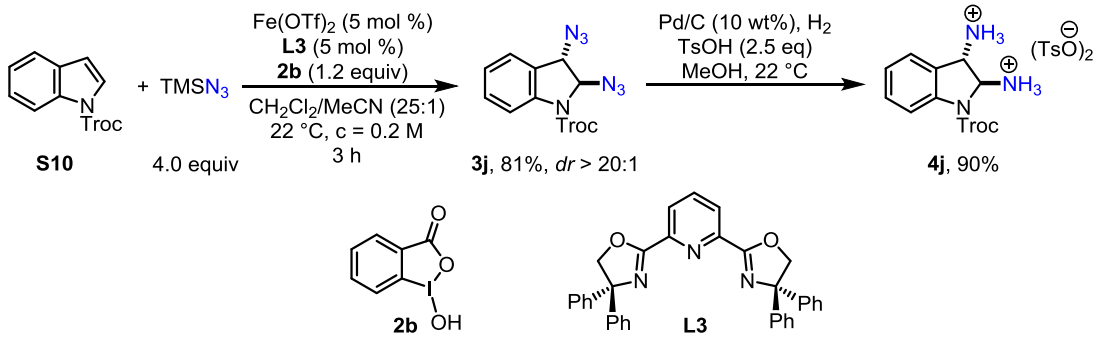
twice with N_2, a solution of diazidation product **3i** (117.2 mg, 0.3 mmol, dissolved in 5 mL MeOH) was added to the vial. The mixture was degassed with brief evacuation and backfilled twice with N_2 and then three times with H_2. The reaction was vigorously stirred under H_2 at room temperature until the reduction completed (the reaction was monitored by IR until the absorption of azido groups disappeared). The solution was filtered through Celite and washed with MeOH. The filtrate was concentrated *in vacuo*, dissolved in minimum amount of MeOH (about 0.5 mL), and then diluted with Et_2O (10 mL). The white precipitate was collected by filtration, washed with Et_2O (5 mL × 3) and dried *in vacuo*. **4i** was obtained as a white solid (182.4 mg, 89% yield, *dr* > 20:1, m.p. 249–251 ˚C). IR ν_{max} (neat)/cm^{-1}: 2951 (brs), 1721 (m), 1498 (m), 1399 (m), 1170 (s), 1033 (m), 1011 (m), 686 (m); ^{1}H NMR (400 MHz, CD_3OD): δ 8.10 (d, J = 8.5 Hz, 1H), 7.71 (d, J = 8.1 Hz, 4H), 7.59 (d, J = 7.7 Hz, 1H), 7.55–7.48 (m, 1H), 7.32 (t, J = 7.6 Hz, 1H), 7.25 (d, J = 8.0 Hz, 4H), 5.00–4.92 (m, 2H), 4.86 (d, J = 2.6 Hz, 1H), 4.38 (dd, J = 15.5, 5.9 Hz, 1H), 4.27–4.19 (m, 2H), 2.39 (s, 6H); ^{13}C NMR (100 MHz, CD_3OD): δ 152.2, 141.8, 140.6, 137.1, 130.3, 129.9, 128.6, 125.6, 125.5, 123.9, 120.0, 94.9, 75.5, 48.9, 47.7, 42.8, 19.9; HRMS (ESI, m/z): calcd for $C_{12}H_{15}Cl_3N_3O_2^+$, [M + H^+], 338.0224, found 338.0230.



S10, 88%

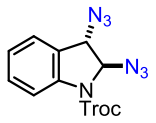
2,2,2-Trichloroethyl-1*H*-indole-1-carboxylate (**S10**). To a solution of indole (234.4 mg, 2.0 mmol) in CH_2Cl_2 (10 mL) cooled in an ice-water bath, Bu_4NHSO_4 (34 mg, 0.1 mmol) and NaOH (320 mg, 8.0 mmol) were added, followed by drop-wise addition of 2,2,2-trichlorethoxycarbonyl chloride (0.41 mL, 3.0 mmol). The reaction was allowed to warm up to room temperature gradually, and stirred for 2 h until indole was consumed. Then the reaction mixture was diluted with water (50 mL) and extracted with CH_2Cl_2 (25 mL × 3). The combined

organic layer was washed with brine (25 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified through a silica gel flash column (hexanes/EtOAc = 10:1) to afford the *N*-Troc indole **S10** as a white solid (514.8 mg, 88% yield). IR ν_{max} (neat)/cm^{-1}: 2961 (w), 1739 (s), 1536 (w), 1455 (s), 1391 (s), 1343 (m), 1326 (s), 1236 (s), 1211 (m), 1120 (s) 753 (s), 715 (s); ^{1}H NMR (400 MHz, 310 K, $CDCl_3$): δ 8.28 (d, J = 8.1 Hz, 1H), 7.70 (d, J = 3.7 Hz, 1H), 7.62 (d, J = 7.7 Hz, 1H), 7.51–7.37 (m, 1H), 7.32 (td, J = 7.7, 0.9 Hz, 1H), 6.69 (d, J = 3.7 Hz, 1H), 5.07 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.3, 135.3, 130.8, 125.4, 125.1, 123.7, 121.3, 115.4, 109.4, 94.6, 77.4, 75.8; HRMS (ESI, m/z): calcd for $C_{11}H_9Cl_3NO_2^+$, [M + H^+], 291.9693, found 291.9699.



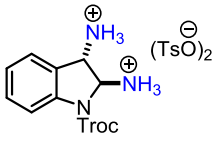
To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stirring bar were added $Fe(OTf)_2$ (8.9 mg, 0.025 mmol) and **L3** (13.1 mg, 0.025 mmol). After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (0.8 mL) and MeCN (0.2 mL) were added via a syringe and the mixture was stirred at room temperature for 10 min. To another flame-dried 3-dram vial (vial **B**) equipped with a stirring bar were added **2b** (158.4 mg, 0.60 mmol) and *N*-Troc indole **S10** (146.0 mg, 0.5 mmol). This vial was evacuated and backfilled with N_2 three times and anhydrous CH_2Cl_2 (1.5 mL) was added. Both vials were degassed with brief evacuation and backfilled with N_2 twice. $TMSN_3$ (263 µl, 2.0 mmol) was added to vial **B** and followed by drop-wise addition of the catalyst solution in vial **A** at room temperature. The reaction was kept at

room temperature for 3 h and then quenched with saturated $NaHCO_3$ solution (0.1 mL), and further diluted with hexanes (5 mL). The mixture was stirred vigorously for 10 min and filtered through a short silica gel pad. The filtrate was concentrated *in vacuo*. The residue was subsequently purified through a silica gel flash column (hexanes/Et_2O: from 200:1 to 15:1) as white solid (151.8 mg, 81% yield, *dr* > 20:1).



3j

2,2,2-Trichloroethyl-*trans*-2,3-diazidoindoline-1-carboxylate (**3j**): IR ν_{max} (neat)/cm^{-1}: 2102 (s), 1737(w), 1605 (m), 753 (s); ^{1}H NMR (400 MHz, CD_3CN, 318 K): δ 7.85 (d, J = 8.0 Hz, 1H), 7.56–7.46 (m, 2H), 7.24 (t, J = 7.5 Hz, 1H), 5.87 (s, 1H), 5.10 (d, J = 12.2 Hz, 1H), 4.98 (d, J = 12.1 Hz, 1H), 4.83 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, 318 K): δ 150.4, 139.9, 131.1, 131.0, 126.3, 124.5, 115.2, 94.9, 79.8, 74.8, 64.2; HRMS (ESI, m/z): calcd for $C_{11}H_8Cl_3N_7O_2Na^+$, [M + Na^+], 397.9697, found 397.9691.

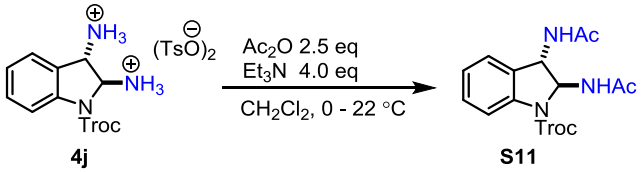


4j

(±)-(2*S*,3*S*)-1-((2,2,2-Trichloroethoxy)carbonyl)indoline-2,3-diaminium ditosylate (**4j**). To a 3-dram vial equipped with a stir bar were added Pd/C (11.3 mg, 10 wt%) and $TsOH·H_2O$ (142.7 mg, 0.75 mmol). After the vial was evacuated and backfilled twice with N_2, a solution of diazidation product **3j** (113.0 mg, 0.3 mmol, dissolved in 5 mL MeOH) was added to the vial. The mixture was degassed with brief evacuation and backfilled twice with N_2 and then three times with H_2. The reaction was vigorously stirred under H_2 at room temperature until the reduction completed (the reaction was monitored by IR until the absorption of azido groups

disappeared). The solution was filtered through Celite and washed with MeOH. The filtrate was concentrated *in vacuo*, dissolved in minimum amount of MeOH (ca. 0.5 mL), and then diluted with Et_2O (10 mL). The white precipitate was collected by filtration, washed with Et_2O (5 mL × 3) and dried *in vacuo*. **4j** was obtained as a white solid (180.1 mg, 90% yield, *dr* > 20:1, m.p. 145–146 ˚C). IR ν_{max} (neat)/cm^{-1}: 2923 (s), 1721 (s), 1599 (m), 1489 (s), 1409 (m), 1328 (m), 1164 (s), 1125 (s), 1035 (s), 1010 (s), 683 (s); ^{1}H NMR (400 MHz, DMSO-*d*6, 318 K): δ 8.64 (brs, 3H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.57 (m, 1H), 7.52 (d, *J* = 8.0 Hz, 4H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 4H), 5.62 (s, 1H), 5.23 (d, *J* = 12.1 Hz, 1H), 5.01 (brs, 1H), 4.87 (s, 1H), 2.30 (s, 6H); ^{13}C NMR (100 MHz, DMSO-*d*6, 318 K): δ 150.6, 148.8, 144.5, 141.0, 140.2, 138.2, 131.4, 128.2, 127.1, 126.9, 125.4, 124.7, 124.3, 115.6, 114.9, 94.5, 75.4, 74.4, 68.8, 54.0, 53.4, 20.7; HRMS (ESI, m/z): calcd for $C_{11}H_{13}N_3O_2Cl_3^+$, [M + H^+], 324.0068, found 324.0057.

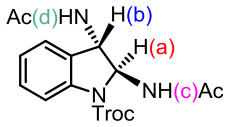
4j was converted to **S11** for *NOE* analysis for relative stereochemistry determination.



4j **S11**

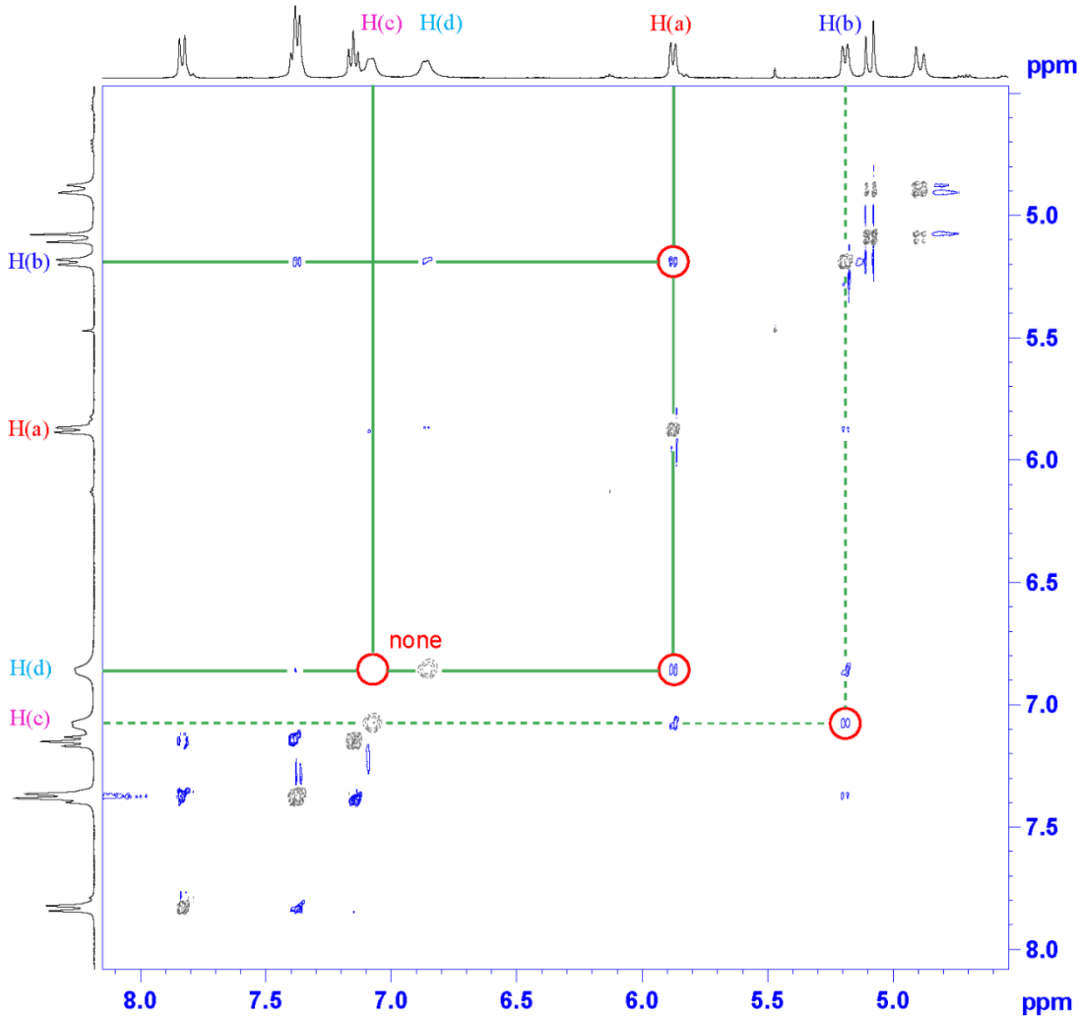
(±)-2,2,2-Trichloroethyl (2*S*,3*S*)-2,3-diacetamidoindoline-1-carboxylate (S11). Diaminium tosylate **4j** (66.9 mg, 0.1 mmol) was suspended in anhydrous CH_2Cl_2 (3 mL) in a flame-dried vial under N_2. The reaction was cooled to 0 °C under stirring. Et_3N (56 µL, 0.4 mmol) was added via a syringe followed by dropwise addition of Ac_2O (23.6 µL, 0.25 mml). The reaction was then warmed up to room temperature and kept stirring for 2 hours. After quenching with saturated $NaHCO_3$ solution under vigorous stirring, the mixture was extracted with CH_2Cl_2 (2 mL × 3) and concentrated *in vacuo*. The crude product was purified through a silica gel column (hexanes/acetone for 3:1 to 1:1) to afford **S11** as a white solid (31.9 mg, 78%

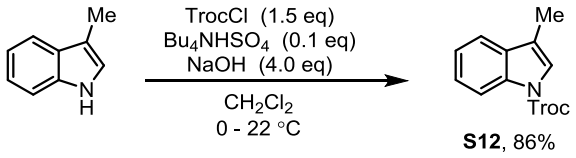
yield). IR ν_{max} (neat)/cm^{-1}: 2921 (s), 2851 (s), 1732 (w), 1555 (m), 1463 (m); ^{1}H NMR (400 MHz, CD_3CN, 318 K): δ 7.83 (d, J = 8.4 Hz, 1H), 7.42–7.33 (m, 2H), 7.14 (t, J = 7.5 Hz, 1H), 7.06 (brd, J = 5.8 Hz, 1H), 6.84 (brd, J = 5.8 Hz, 1H), 5.87 (d, J = 7.7 Hz, 1H), 5.18 (d, J = 7.9 Hz, 1H), 5.09 (d, J = 12.2 Hz, 1H), 4.89 (d, J = 11.9 Hz, 1H), 1.89 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN, 318 K): δ 170.4, 170.0, 152.0, 142.9, 131.4, 130.6, 126.7, 125.1, 116.1, 96.4, 75.9, 73.3, 58.0, 23.4, 23.2; HRMS (ESI, m/z): calcd for $C_{15}H_{17}N_3O_4Cl_3^+$, [M + H$^+$], 408.0279, found 408.0273.



S11

A strong *NOE* was observed between H(a) and H(b); however, there is no significant *NOE* observed between H(c) and H(d). Additionally, *NOE*s between H(a) and H(d), and between H(b) and H(c) were also observed.

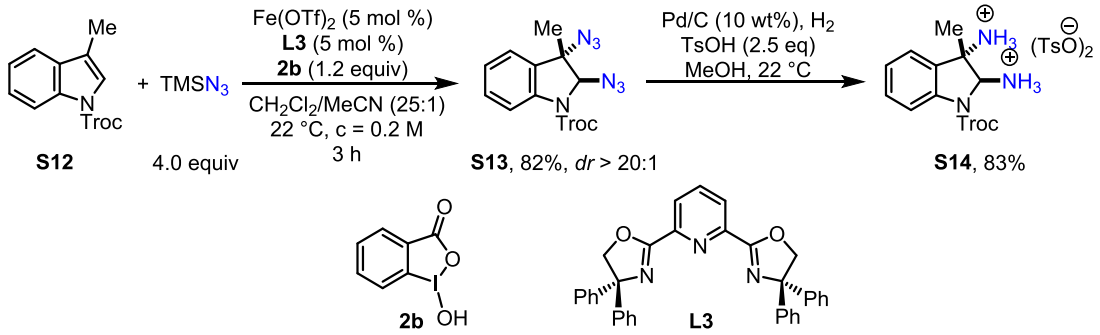




S12, 86%

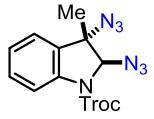
2,2,2-Trichloroethyl-3-methyl-1*H*-indole-1-carboxylate (**S12**). To a solution of 3-methyl indole (262.4 mg, 2.0 mmol) in CH_2Cl_2 (10 mL) cooled in an ice-water bath, Bu_4NHSO_4 (34 mg, 0.1 mmol) and NaOH (320 mg, 8.0 mmol) were added, followed by dropwise addition of 2,2,2-trichlorethoxycarbonyl chloride (0.41 mL, 3.0 mmol). The reaction was allowed to warm up to room temperature gradually, and stirred for 2 h until 3-methyl indole was consumed.

Then the reaction mixture was diluted with water (50 mL) and extracted with CH_2Cl_2 (25 mL × 3). The combined organic layer was washed with brine (25 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified through a silica gel flash column (hexanes/EtOAc = 10:1) to afford **S12** as a white solid (527.4 mg, 86% yield). IR ν_{max} (neat)/cm^{-1}: 2956 (w), 1739 (s), 1612 (w), 1456 (s), 1397 (s), 1348 (m), 1305 (s), 1233 (s), 1152 (m), 1099 (s), 753 (s), 713 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, J = 5.1 Hz, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.44 (s, 1H), 7.44–7.37 (m, 1H), 7.36–7.29 (m, 1H), 5.05 (s, 2H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.1, 135.6, 131.8, 125.0, 123.4, 122.0, 119.3, 118.6, 115.3, 94.7, 75.6, 9.7; HRMS (ESI, m/z): calcd for $C_{12}H_{11}Cl_3NO_2^+$, [M + H^+], 305.9850, found 305.9861.



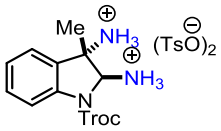
To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stirring bar were added $Fe(OTf)_2$ (8.9 mg, 0.025 mmol) and **L3** (13.1 mg, 0.025 mmol). After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (0.8 mL) and MeCN (0.2 mL) were added via a syringe and the mixture was stirred at room temperature for 10 min. To another flame-dried 3-dram vial (vial **B**) equipped with a stirring bar were added **2b** (158.4 mg, 0.60 mmol) and *N*-Troc-3-methyl indole **S12** (153 mg, 0.5 mmol). This vial was evacuated and backfilled with N_2 three times and anhydrous CH_2Cl_2 (1.5 mL) was added. Both vials were degassed with brief evacuation and backfilled with N_2 twice. $TMSN_3$ (263 μl, 2.0 mmol) was added to vial **B** and followed by drop-wise addition of the catalyst solution in vial **A** at room temperature. The

reaction was kept at room temperature for 3 h and then quenched with saturated $NaHCO_3$ solution (0.1 mL), and further diluted with hexanes (5 mL). The mixture was stirred vigorously for 10 min and filtered through a short silica gel pad. The filtrate was concentrated *in vacuo*. The residue was subsequently purified through a silica gel flash column (hexanes/Et_2O: from 200:1 to 15:1) as a white solid (160.0 mg, 82% yield, *dr* > 20:1). The relative stereochemistry was determined through NOE analysis of a derivatization product of **S13**.



S13

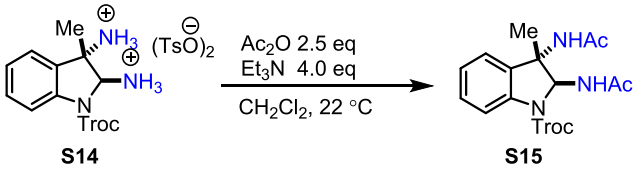
2,2,2-Trichloroethyl-*trans*-2,3-diazido-3-methylindoline-1-carboxylate (**S13**): IR ν_{max} (neat)/cm^{-1}: 2113 (s), 1736 (s), 1483 (m), 1403 (m), 1256 (w), 753 (w); ^{1}H NMR (400 MHz, CD_3CN, 318 K): δ 7.86 (d, J = 7.9 Hz, 1H), 7.57–7.44 (m, 2H), 7.28 (td, J = 7.6, 0.8 Hz, 1H), 5.81 (s, 1H), 5.14 (d, J = 12.2 Hz, 1H), 5.02 (d, J = 12.1 Hz, 1H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, DMSO-*d*6, 318 K): δ 150.3, 139.1, 130.9, 129.6, 124.4, 123.5, 115.1, 94.9, 82.6, 74.7, 69.5, 16.8.



S14

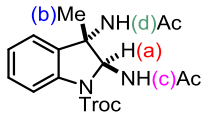
(±)-(2*S*,3*S*)-1-((2,2,2-Trichloroethoxy)carbonyl)indoline-3-methyl-2,3-diaminium ditosylate ditosylate (**S14**). To a 3-dram vial equipped with a stir bar were added Pd/C (11.7 mg, 10 wt%) and $TsOH \cdot H_2O$ (142.7 mg, 0.75 mmol). After the vial was evacuated and backfilled twice with N_2, a solution of diazidation product **S13** (117.2 mg, 0.3 mmol, dissolved in 5 mL MeOH) was added to the vial. The mixture was degassed with brief evacuation and backfilled twice with N_2 and then three times with H_2. The reaction was vigorously stirred under H_2 at room

temperature until the reduction completed (the reaction was monitored by IR until the absorption of azido groups disappeared). The solution was filtered through Celite and washed with MeOH. The filtrate was concentrated *in vacuo*, dissolved in minimum amount of MeOH (ca. 0.5 mL), and then diluted with Et_2O (10 mL). The white precipitate was collected by filtration, washed with Et_2O (5 mL × 3) and dried *in vacuo*. **S14** was obtained as a white solid (171.2 mg, 83% yield, *dr* > 20:1, decomposed at 234˚C). IR ν_{max} (neat)/cm^{-1}: 2855 (s), 1731 (s), 1532 (w), 1484 (m), 1398 (w), 1325 (w), 1192 (s), 1124 (s), 1039 (s), 1010 (s), 762 (m), 682 (s); ^{1}H NMR (400 MHz, DMSO-*d*6, 318 K): δ 8.71 (brs, 3H), 7.76 (d, *J* = 7.3 Hz, 1H), 7.64–7.55 (m, 2H), 7.52 (d, *J* = 8.0 Hz, 4H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 7.9 Hz, 4H), 5.58 (s, 1H), 5.24 (d, *J* = 12.1 Hz, 1H), 5.01 (d, *J* = 12.0 Hz, 1H), 2.32 (s, 6H), 1.84 (s, 3H); ^{13}C NMR (100 MHz, DMSO-*d*6, 318 K): δ 150.3, 144.9, 139.4, 138.0, 131.5, 128.5, 128.0, 125.4, 125.0, 124.8, 115.6, 94.7, 75.2, 71.9, 60.3, 20.6, 16.9; HRMS (ESI, m/z): calcd for $C_{12}H_{15}O_2N_3Cl_3^+$, [M + H^+], 338.0224, found 338.0209.



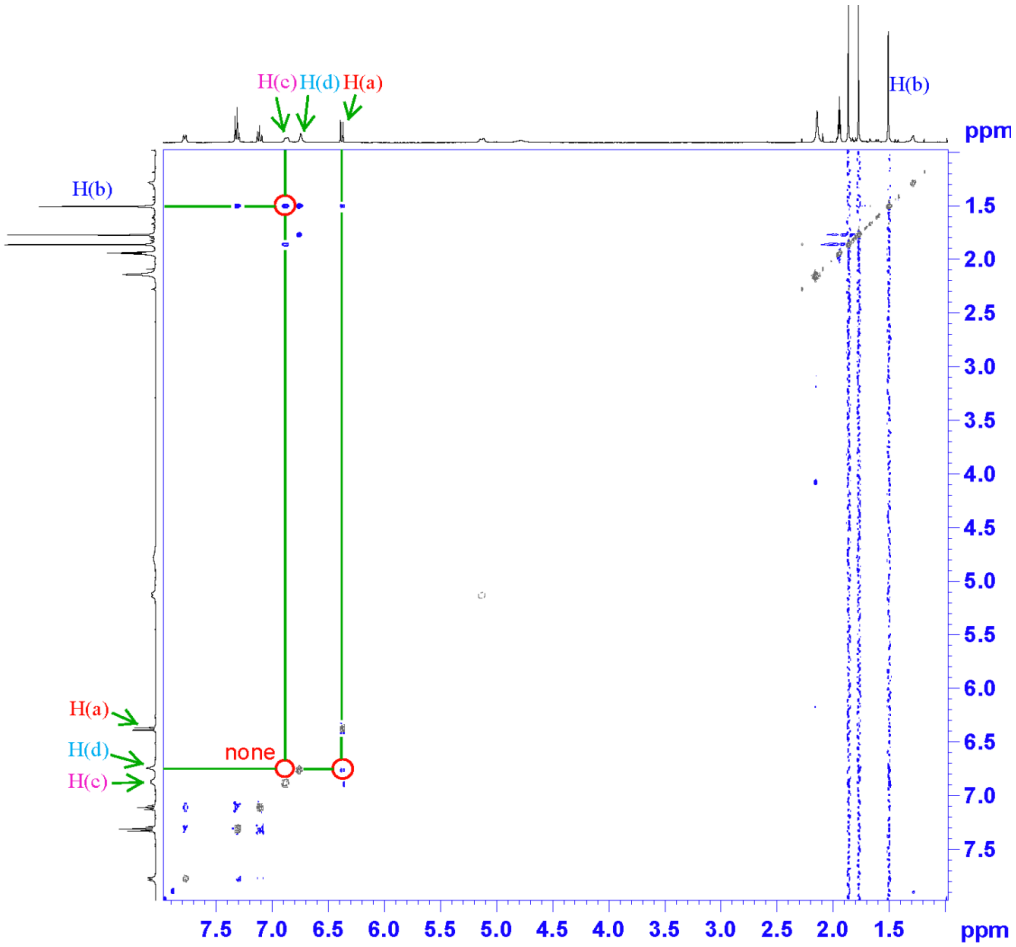
(±)-2,2,2-Trichloroethyl (2*S*,3*S*)-2,3-diacetamidoindoline-1-carboxylate (S15). Diaminium tosylate **S14** (66.9 mg, 0.1 mmol) was suspended in anhydrous CH_2Cl_2 (3 mL) in a flame-dried vial under N_2. The reaction was cooled to 0 °C under stirring. Et_3N (56 µL, 0.4 mmol) was added via a syringe followed by drop-wise addition of Ac_2O (23.6 µL, 0.25 mml). The reaction was then warmed up to room temperature and kept stirring for 2 hours. After quenching with saturated $NaHCO_3$ solution under vigorous stirring, the mixture was extracted with CH_2Cl_2 (2 mL × 3) and concentrated *in vacuo*. The crude product was purified through a silica gel flash column (hexanes/acetone from 3:1 to 1:1) to afford **S15** as a white solid (22.0 mg,

52% yield). IR ν_{max} (neat)/cm^{-1}: 3275 (m), 2922 (m), 1726 (s), 1653 (s), 1543 (s), 1485 (s), 1403 (s); ^{1}H NMR (400 MHz, CD_3CN): δ 7.80 (d, J = 8.1 Hz, 1H), 7.36–7.30 (m, 2H), 7.17–7.10 (m, 1H), 6.89 (d, J = 8.2 Hz, 1H), 6.76 (s, 1H), 6.40 (d, J = 8.8 Hz, 1H), 5.15 (d, J = 12.4 Hz, 1H), 4.79 (s, 1H), 1.88 (s, 3H), 1.79 (s, 3H), 1.52 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN): δ 169.4, 169.1, 151.0, 141.5, 134.2, 129.1, 123.7, 123.5, 114.8, 95.2, 74.6, 72.9, 61.9, 22.4, 22.1, 20.3; HRMS (ESI, m/z): calcd for $C_{16}H_{19}N_3O_4Cl_3^+$, [M + H^+], 422.0436, found: 422.0426.



S15

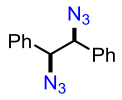
A strong *NOE* was observed between H(c) and H(b); however, there is no significant *NOE* observed between H(c) and H(d). Additionally, *NOE*s between H(a) and H(d), and between H(c) and H(b) were also observed.



trans-Stilbene **10b** is commercially available and it was further purified upon recrystallization before usage.

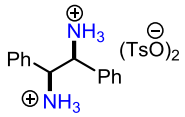
To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stirring bar were added $Fe(OTf)_2$ (8.9 mg, 0.025 mmol) and **L3** (13.1 mg, 0.025 mmol). After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (0.8 mL) and MeCN (0.2 mL) were added via

a syringe and the mixture was stirred at room temperature for 10 min. To another flame-dried 3-dram vial (vial **B**) equipped with a stirring bar were added **2b** (158.4 mg, 0.60 mmol) and *trans*-stilbene **10b** (90.1 mg, 0.5 mmol). This vial was evacuated and backfilled with N_2 three times and anhydrous CH_2Cl_2 (4.0 mL) was added. Both vials were degassed with brief evacuation and backfilled with N_2 twice. $TMSN_3$ (263 µL, 2.0 mmol) was added to vial **B** and followed by drop-wise addition of the catalyst solution in vial **A** at room temperature. The reaction was kept at room temperature for 3 h and then quenched with a saturated $NaHCO_3$ solution (0.1 mL) and further diluted with hexanes (5 mL). The mixture was stirred vigorously for additional 10 min and filtered through a short silica gel pad. The filtrate was concentrated *in vacuo*. The residue was subsequently purified through a silica gel flash column (hexanes/Et_2O: from 200:1 to 50:1) as a colorless oil (113.6 mg, 86% yield, *dr* = 2.5:1). Lower *dr* (1.5:1) was obtained when the $Fe(OAc)_2$–**L3** complex was used as the catalyst.



11, *dr* = 2.5:1

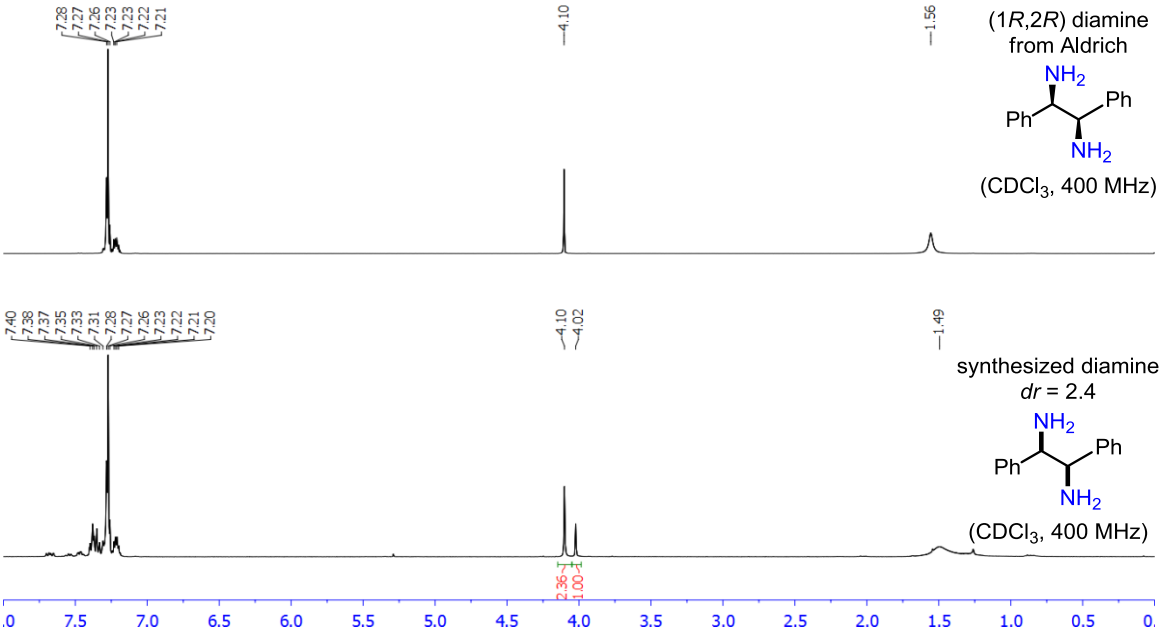
1,2-Diazido-1,2-diphenylethane (**11**): IR ν_{max} (neat)/cm^{-1}: 2959 (w), 2100 (s), 1252(m), 1116 (w), 842 (m); ^1H NMR (400 MHz, $CDCl_3$): δ 7.41 (m, 6H, minor), 7.35–7.19 (m, 4H, minor and m, 6H, major), 7.10 (m, 4H, major), 4.72 (s, 2H, minor), 4.67 (s, 2H, major); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.0 (minor), 135.9 (major), 129.1 (minor), 128.83 (minor), 128.79 (major), 128.7 (major), 128.1 (minor), 127.8 (major), 70.9 (major), 69.8 (minor).

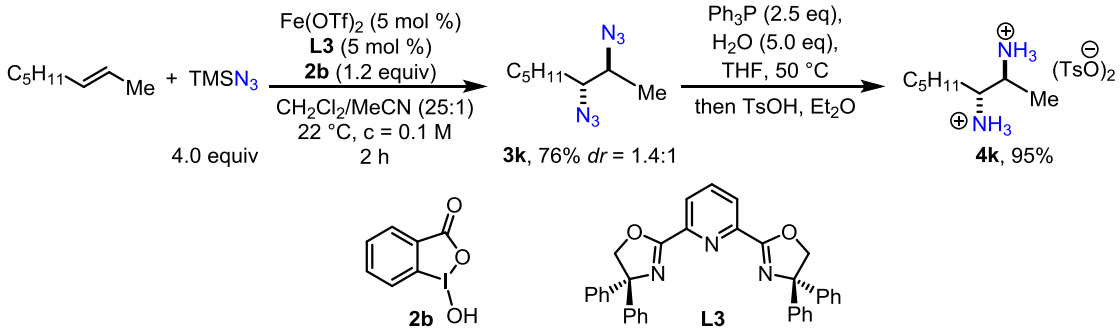


S16, *dr* = 2.5:1

1,2-Diphenylethane-1,2-diaminium ditosylate (**S16**). To a 3-dram vial equipped with a stir bar were added diazidation product **11** (79.3 mg, 0.3 mmol), THF (3 mL) and H_2O (27 μL, 1.5 mmol). After the vial was evacuated and backfilled with N_2 three times, a solution of PPh_3 (196.8 mg, 0.75 mmol) in THF (1.5 mL) was added drop-wise at 0 °C. The mixture was warmed up to 50 °C and stirred for 6 h (the reaction was monitored by IR until the absorption of azido groups disappeared). The mixture was then concentrated *in vacuo* and the residue was further dissolved in Et_2O (5 mL). This solution was added drop-wise to another solution of $TsOH{\cdot}H_2O$ (142.7 mg, 0.75 mmol) in Et_2O (3 mL). The reaction was kept stirring for 30 min and the white precipitate was collected by filtration, washed with Et_2O (5 mL × 3) and dried *in vacuo*. **S16** was obtained as a white solid (138.6 mg, 83% yield, *dr* = 2.5:1, m.p. 251–253 ˚C). IR ν_{max} (neat)/cm^{-1}: 2911 (s), 2662 (m), 1599 (w), 1538 (m), 1171 (s), 1157 (s), 1123 (s), 1032 (s), 1007 (s), 811 (m), 698 (m), 679 (s); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.83 (s, 6H, major), 8.43 (s, 6H, minor), 7.72–7.67 (m, 4H, minor), 7.55 (d, J = 8.0 Hz, 4H), 7.57–7.42 (m, 6H, minor), 7.36–7.27 (m, 6H, major), 7.27–7.22 (m, 4H, minor), 7.18 (d, J = 7.8 Hz, 4H), 4.92 (s, 2H, major), 4.77 (s, 2H, minor), 2.31 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 144.8, 138.4, 133.2, 132.6, 130.0, 129.38, 129.35, 128.69, 128.65, 128.62, 128.4, 125.6, 56.9 (major), 56.7 (minor), 20.9; HRMS (ESI, m/z): calcd for $C_{14}H_{17}N_2^+$, [M + H^+], 213.1386, found 213.1382.

The relative stereochemistry of the major diastereomer was determined by comparison of the ^{1}H NMR spectrum of the synthetic diamines with the one obtained from commercially available (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine (Aldrich 364010).

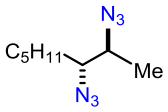




trans-2-Octene is commercially available and it was distilled before usage.

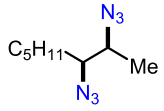
To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stirring bar were added $Fe(OTf)_2$ (8.9 mg, 0.025 mmol) and **L3** (13.1 mg, 0.015 mmol). After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (0.8 mL) and MeCN (0.2 mL) were added via a syringe and the mixture was stirred at room temperature for 10 min. To another flame-dried 3-dram vial (vial **B**) equipped with a stirring bar was added **2b** (158.4 mg, 0.60 mmol). This vial was evacuated and backfilled with N_2 three times and anhydrous CH_2Cl_2 (4.0 mL) was added. Both vials were degassed with brief evacuation and backfilled with N_2 twice. Freshly distilled

trans-2-octene (78 μL, 0.5 mmol), $TMSN_3$ (263 μL, 2.0 mmol) were added successively to vial **B** and followed by drop-wise addition of the catalyst solution in vial **A** at room temperature. The reaction was kept at room temperature for 2 h and then quenched with saturated $NaHCO_3$ solution (0.1 mL) and further diluted with hexanes (5 mL). The mixture was stirred vigorously for additional 10 min and filtered through a short silica gel pad. The filtrate was concentrated *in vacuo*. The residue was subsequently purified through a silica gel flash column (hexanes/Et_2O: from 200:1 to 50:1) as colorless oil (74.6 mg, 76% yield, *dr* = 1.4:1). *anti*- and *syn*-**3k** were separated through a silica gel flash column (hexanes/Et_2O: from 200:1 to 50:1).



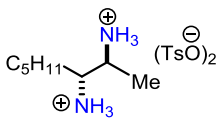
anti-**3k**

***anti*-2,3-Diazidooctane** (*anti*-**3k**): IR ν_{max} (neat)/cm^{-1}: 2931 (m), 2097 (s), 1251 (m), 1153 (m), 744 (w); ^1H NMR (400 MHz, $CDCl_3$): δ 3.63–3.48 (m, 1H), 3.31 (dt, *J* = 9.0, 4.6 Hz, 1H), 1.55–1.48 (m, 3H), 1.41–1.25 (m, 8H), 0.91 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 66.5, 60.4, 31.6, 30.9, 26.1, 22.6, 14.6, 14.1.



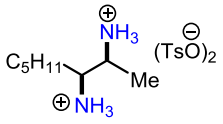
syn-**3k**

***syn*-2,3-Diazidooctane** (*syn*-**3k**): IR ν_{max} (neat)/cm^{-1}: 2932 (m), 2091 (s), 1454 (w), 1249 (m), 1055 (m), 1009 (m); ^1H NMR (400 MHz, $CDCl_3$): δ 3.56–3.47 (m, 1H), 3.21–3.13 (m, 1H), 1.68–1.55 (m, 2H), 1.55–1.43 (m, 2H), 1.37–1.29 (m, 7H), 0.91 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 66.5, 60.3, 31.6, 31.1, 25.9, 22.6, 16.5, 14.1.



anti-**4k**

***anti*-Octane-2,3-diaminium ditosylate** (*anti*-**4k**). To a 3-dram vial equipped with a stir bar were added diazidation product *anti*-**3k** (58.9 mg, 0.3 mmol), THF (3 mL) and H_2O (27 μL, 1.5 mmol). After the vial was evacuated and backfilled with N_2 three times, a solution of PPh_3 (196.8 mg, 0.75 mmol) in THF (1.5 mL) was added drop-wise at 0 °C. The mixture was warmed up to 50 °C and stirred for 6 h (the reaction was monitored by IR until the absorption of azido groups disappeared). The mixture was then concentrated *in vacuo* and the residue was further dissolved in Et_2O (5 mL). This solution was added drop-wise to another solution of $TsOH{\cdot}H_2O$ (142.7 mg, 0.75 mmol) in Et_2O (3 mL). The reaction was kept stirring for 30 min and the white precipitate was collected by filtration, washed with Et_2O (5 mL × 3) and dried *in vacuo*. *anti*-**4k** was obtained as a white solid (139.3 mg, 95% yield, m.p. 278–279 ˚C). IR ν_{max} (neat)/cm^{-1}: 2951 (s), 2923 (s), 2866 (s), 1622 (m), 1532 (m), 1172 (s), 1122 (s), 1035 (s), 1010 (s), 813 (m), 677 (s); ^{1}H NMR (400 MHz, CD_3OD): δ 7.71 (d, J = 8.2 Hz, 4H), 7.25 (d, J = 8.0 Hz, 4H), 3.64 (qd, J = 6.9, 4.8 Hz, 1H), 3.47 (dt, J = 8.1, 5.0 Hz, 1H), 2.37 (s, 6H), 1.81–1.57 (m, 2H), 1.54–1.43 (m, 1H), 1.39 (d, J = 6.9 Hz, 3H), 1.35–1.31 (m, 5H), 0.91 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 143.2, 141.9, 129.9, 126.9, 55.1, 49.8, 32.5, 30.5, 25.8, 23.4, 21.3, 14.5, 14.3; HRMS (ESI, m/z): calcd for $C_8H_{21}N_2^+$, [M + H^+], 145.1699, found 145.1695.

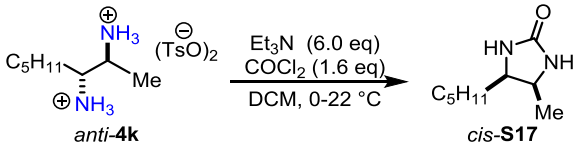


syn-**4k**

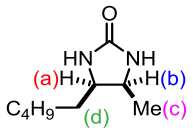
***syn*-Octane-2,3-diaminium ditosylate** (*syn*-**4k**). By following the same reduction procedure, the diamine salt *syn*-**4k** was also obtained as a white solid (139.3 mg, 95% yield, m.p. 278–279 ˚C). IR ν_{max} (neat)/cm^{-1}: 2951 (s), 2923 (s), 2866 (s), 1622 (m), 1532 (m), 1172 (s), 1122 (s), 1035 (s), 1010 (s), 813 (m), 677 (s); ^{1}H NMR (400 MHz, CD_3OD): δ 7.71 (d, J = 8.1 Hz, 4H), 7.24 (d, J = 7.9 Hz, 4H), 3.84–3.67 (m, 1H), 3.55 (dt, J = 7.5, 3.5 Hz, 1H), 2.37 (s, 6H),

1.77–1.66 (m, 1H), 1.66–1.55 (m, 1H), 1.55–1.42 (m, 1H), 1.40–1.27 (m, 8H), 0.91 (t, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 143.3, 141.9, 129.9, 126.9, 54.0, 49.5, 32.6, 27.7, 26.1, 23.4, 21.3, 14.3, 13.1; HRMS (ESI, m/z): calcd for $C_8H_{21}N_2^+$, [M + H^+], 145.1699, found 145.1695.

The relative stereochemistry of two isomers of **4k** was determined by *NOE* analysis of their corresponding ureas after derivatization.

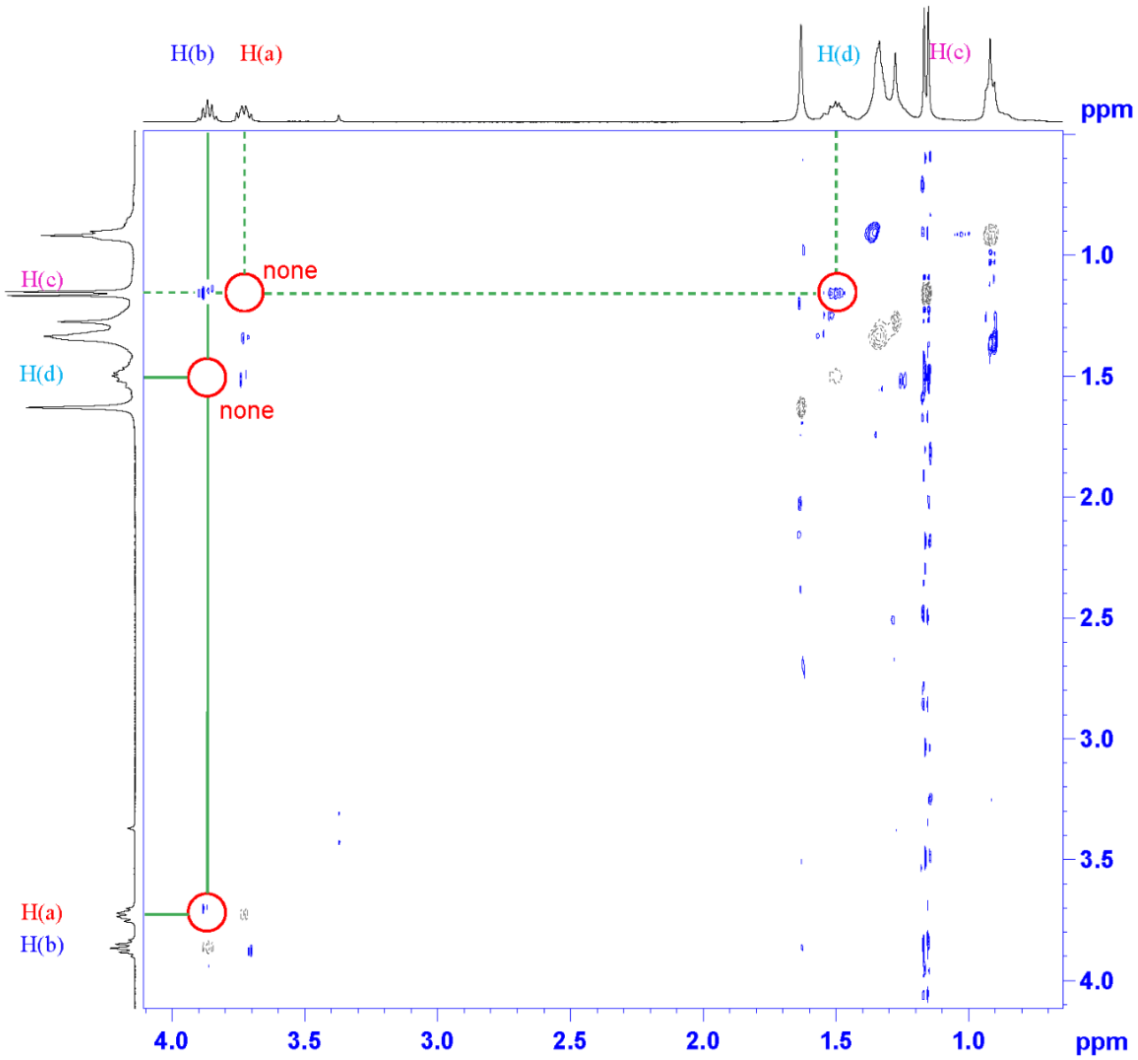


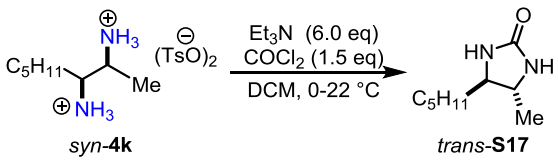
***cis*-4-Methyl-5-pentylimidazolidin-2-one** (*cis*-**S17**). Octane-2,3-diamonium ditosylate *anti*-**4k** (24.5 mg, 0.05 mmol) was suspended in anhydrous CH_2Cl_2 (2 mL) in a flame-dried vial under N_2. The mix was cooled to 0 °C under stirring. Et_3N (42 µL, 0.3 mmol) was added via a syringe followed by drop-wise addition of a phosgene toluene solution (57.1 µL, 0.08 mmol, 15 wt%). The reaction was then warmed up to room temperature and kept stirring for 3 hours. After quenching with the saturated $NaHCO_3$ solution under vigorous stirring, the mixture was extracted with CH_2Cl_2 (2 mL × 3) and concentrated *in vacuo*. The crude product was purified through a silica gel column (hexanes/acetone from 2:1 to 1:1) to afford the product *cis*-**S17** as a solid (7.2 mg, 84% yield). IR ν_{max} (neat)/cm^{-1}: 3205 (m), 2926 (m), 2856 (m), 1697 (s), 1454 (m), 1373 (w), 1254 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.54 (brs, 1H), 4.38 (brs, 1H), 3.89–3.79 (m, 1H), 3.75–3.66 (m, 1H), 1.54–1.41 (m, 2H), 1.39–1.26 (m, 6H), 1.14 (d, J = 6.5 Hz, 3H), 0.90 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 56.1, 51.4, 31.7, 29.6, 26.2, 22.5, 15.8, 14.0; HRMS (ESI, m/z): calcd for $C_9H_{19}N_2O^+$, [M + H^+], 171.1492, found 171.1484.



cis-**S17**

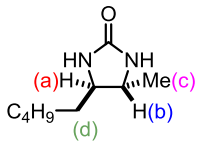
The strong *NOE* between the methyl H(c) and the methylene H(d) was observed.





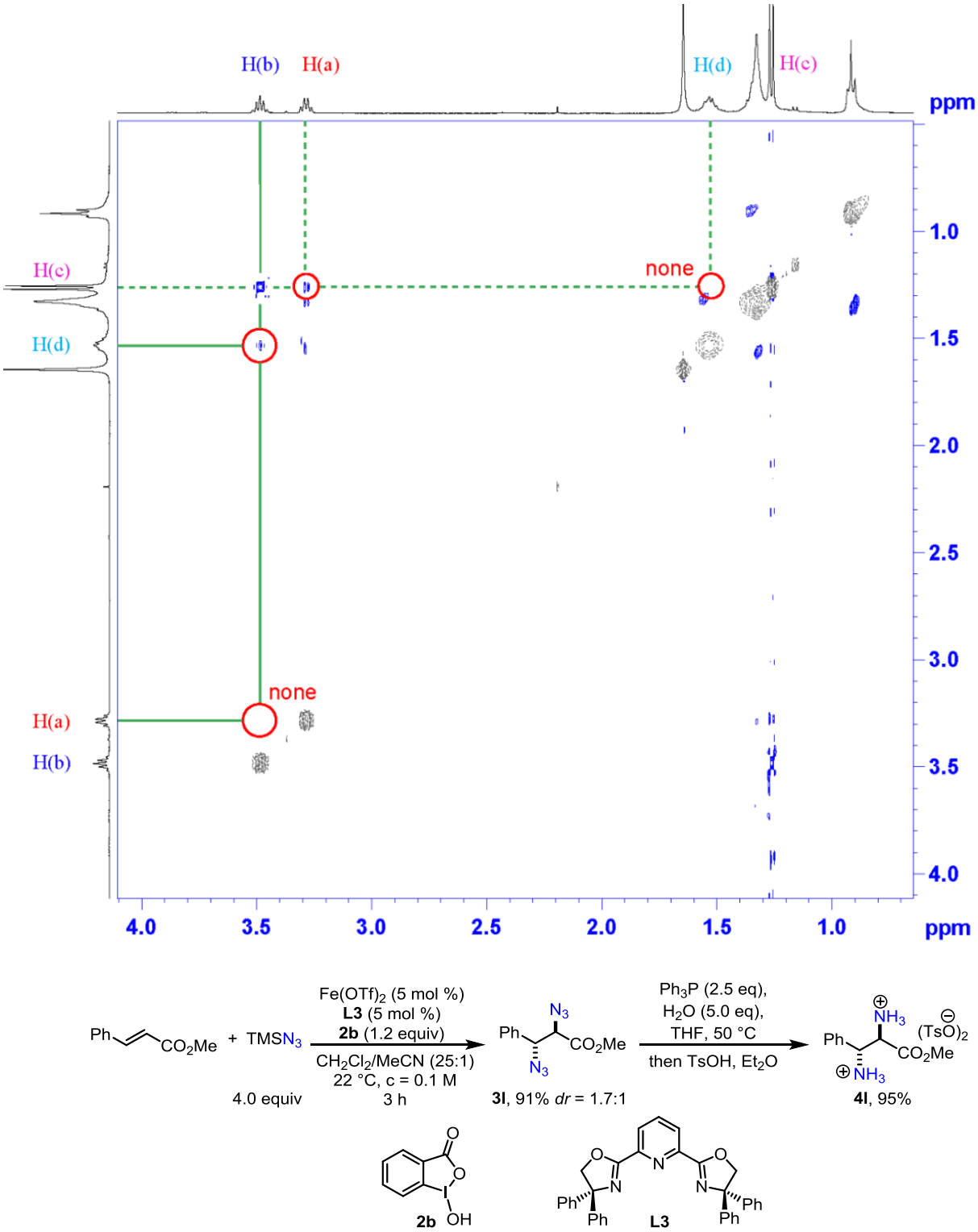
syn-**4k** *trans*-**S17**

***trans*-4-Methyl-5-pentylimidazolidin-2-one** (*trans*-**S17**). By following the same procedure, *trans*-**S17** was prepared through *syn*-**4k** and isolated as colorless oil (6.9 mg, 81% yield). IR ν_{max} (neat)/cm^{-1}: 3206 (m), 2926 (m), 2855 (m), 1697 (s), 1454 (m), 1374 (w), 1254 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.62 (brs, 1H), 4.53 (brs, 1H), 3.56–3.43 (m, 1H), 3.33–3.23 (m, 1H), 1.60–1.46 (m, 2H), 1.35 (d, J = 15.7 Hz, 6H), 1.26 (d, J = 6.2 Hz, 3H), 0.92 (t, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4, 60.5, 54.3, 35.1, 31.7, 25.4, 22.5, 21.2, 14.0; HRMS (ESI, m/z): calcd for $C_9H_{19}N_2O^+$, [M + H^+], 171.1492, found 171.1484.



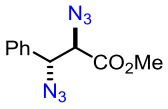
trans-**S17**

There is absence of *NOE* between H(c) and H(d) and the *NOE* between H(b) and H(d) was observed instead.



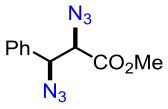
Methyl *trans*-cinnamate is commercially available and it was used directly.

To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stirring bar were added $Fe(OTf)_2$ (8.9 mg, 0.025 mmol) and **L3** (13.1 mg, 0.025 mmol). After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (0.8 mL) and MeCN (0.2 mL) were added via a syringe and the mixture was stirred at room temperature for 10 min. To another flame-dried 3-dram vial (vial **B**) equipped with a stirring bar was added **2b** (158.4 mg, 0.60 mmol) and *trans*-methyl *trans*-cinnamate (81.1 mg, 0.5 mmol). This vial was evacuated and backfilled with N_2 three times and anhydrous CH_2Cl_2 (4.0 mL) was added. Both vials were degassed with brief evacuation and backfilled with N_2 twice. $TMSN_3$ (263 μl, 2.0 mmol) was added to vial **B** and followed by drop-wise addition of the catalyst solution in vial **A** at room temperature. The reaction was kept at room temperature for 3 h and then quenched with saturated $NaHCO_3$ solution (0.1 mL), and further diluted with hexanes (5 mL). The mixture was stirred vigorously for 10 min and filtered through a short silica gel pad. The filtrate was concentrated *in vacuo*. The residue was subsequently purified through a silica gel flash column (hexanes/Et_2O: from 200:1 to10:1). The major diastereomer anti-**3l** and minor diastereomer *syn*-**3l** were both isolated as colorless oil (70.5 mg, 57% yield and 41.5 mg, 34% yield respectively).



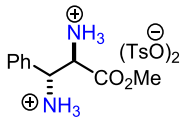
anti-**3l**

***anti*-Methyl-2,3-diazido-3-phenylpropanoate** (*anti*-**3l**): IR ν_{max} (neat)/cm^{-1}: 2099 (s), 1744(m), 1275 (w), 764 (m); ^1H NMR (400 MHz, $CDCl_3$): δ 7.48–7.40 (m, 3H), 7.40–7.33 (m, 2H), 4.90 (d, J = 8.0 Hz, 1H), 4.10 (d, J = 8.0 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 134.6, 129.7, 129.2, 128.0, 65.7, 65.6, 53.2.



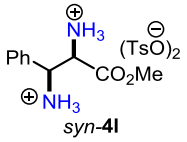
syn-**3l**

***syn*-Methyl-2,3-diazido-3-phenylpropanoate** (*syn*-**3l**): IR ν_{max} (neat)/cm^{-1}: 2105 (s), 1747(m), 1275 (w), 764 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56–7.31 (m, 5H), 5.05 (d, J = 5.7 Hz, 1H), 4.03 (d, J = 5.7 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 135.0, 129.4, 129.1, 127.6, 66.44, 66.40, 53.1.



anti-**4l**

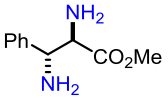
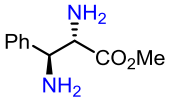
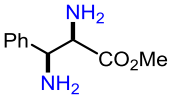
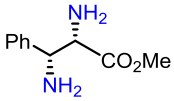
anti*-3-Methoxy-3-oxo-1-phenylpropane-1,2-diaminium ditosylate** (*anti*-4l***). To a 3-dram vial equipped with a stir bar were added diazidation product *anti*-**3l** (73.9 mg, 0.3 mmol), THF (3 mL) and H_2O (27 μL, 1.5 mmol). After the vial was evacuated and backfilled with N_2 three times, a solution of PPh_3 (196.8 mg, 0.75 mmol) in THF (1.5 mL) was added drop-wise at 0 °C. The mixture was warmed up to 50 °C and stirred for 6 h (the reaction was monitored by IR until the absorption of azido groups disappeared). The mixture was then concentrated *in vacuo* and the residue was further dissolved in Et_2O (5 mL). This solution was added drop-wise to another solution of $TsOH{\cdot}H_2O$ (142.7 mg, 0.75 mmol) in Et_2O (3 mL). The reaction was kept stirring for 30 min and the white precipitate was collected by filtration, washed with Et_2O (5 mL × 3) and dried *in vacuo*. *anti*-**4l** was obtained as a white solid (147.5 mg, 91% yield, m.p. 217–219 ˚C). IR ν_{max} (neat)/cm^{-1}: 2859 (s), 2681 (m), 1758 (s), 1552 (w), 1211 (s), 1175 (s), 1125 (s), 1036 (s), 1010 (s), 812 (m), 680 (s); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.64 (brs, 6H), 7.61–7.41 (m, 9H), 7.15 (d, J = 7.7 Hz, 4H), 4.71 (d, J = 8.0 Hz, 1H), 4.51 (d, J = 8.0 Hz, 1H), 3.80 (s, 3H), 2.30 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.7, 145.0, 138.2, 132.1, 130.1, 129.4, 128.33, 128.29, 125.6, 54.7, 53.8, 53.6, 20.9; HRMS (ESI, m/z): calcd for $C_{10}H_{15}O_2N_2^+$ [M + H^+], 195.1128, found 195.1123.

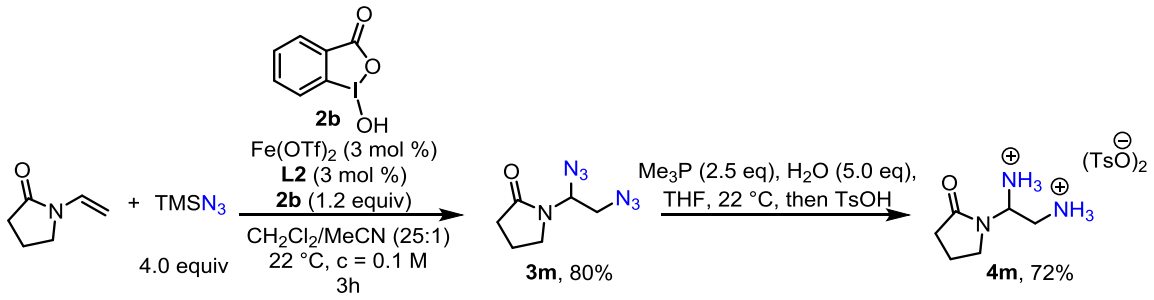


syn-**4l**

syn*-3-Methoxy-3-oxo-1-phenylpropane-1,2-diaminium ditosylate** (*syn*-4*l**). By following the same reduction procedure, the *syn*-diamine salt syn-***4*l** was obtained as a white solid (153.3 mg, 95% yield, m.p. 172–174 ˚C). IR ν_{max} (neat)/cm^{-1}: 3482 (w), 2954 (s), 1756 (s), 1601 (w), 1530 (w), 1172 (s), 1124 (s), 1034 (s), 1010 (s), 816 (m), 683 (s); ^{1}H NMR (400 MHz, DMSO-*d*6): δ 8.72 (brs, 6H), 7.52–7.47 (m, 3H), 7.49 (d, *J* = 7.9 Hz, 4H), 7.37 (dd, *J* = 6.5, 2.8 Hz, 2H), 7.13 (d, *J* = 7.9 Hz, 4H), 4.75 (d, *J* = 4.9 Hz, 1H), 4.61 (d, *J* = 4.5 Hz, 1H), 3.72 (s, 3H), 2.30 (s, 6H); ^{13}C NMR (100 MHz, CD_3OD): 167.2, 143.3, 141.9, 131.9, 130.94, 130.90, 129.9, 129.2, 126.9, 55.6, 55.5, 54.5, 21.3; HRMS (ESI, m/z): calcd for $C_{10}H_{15}O_2N_2^+$, [M + H^+], 195.1128, found 195.1122.

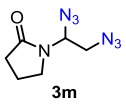
The relative stereochemistry of both diastereomers was determined by comparing the ^{1}H NMR spectra of diamines **S18** with the ones obtained from the literature.[76,77,78] The free diamines were obtained by dissolving the diammonium salts in 2 N NaOH solution and extraction with CH_2Cl_2 for three times.

	 *trans*-**S18**	 (2*S*,3*S*)[6]	 *cis*-**S18**	 (2*S*,3*R*)[7,8]
^{1}H NMR	^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.24 (m, 5H), 4.27 (d, *J* = 5.8 Hz, 1H), 3.72 (d, *J* = 5.8 Hz, 1H), 3.70 (s, 3H), 1.83 (brs, 4H).	^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40–7.20 (m, 5H), 4.24 (d, *J* = 5.9, 1H), 3.70 (d, *J* = 5.9, 1H), 3.68 (s, 3H), 1.95 (brs, 4H).	^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.23 (m, 5H), 4.30 (d, *J* = 4.5 Hz, 1H), 3.67 (s, 3H), 3.65 (d, *J* = 4.5 Hz, 1H), 1.65 (brs, 4H).	^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.25 (m, 5H), 4.30 (d, *J* = 4.5 Hz, 1H), 3.67 (s, 3H), 3.65 (d, *J* = 4.8 Hz, 1H).



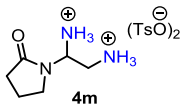
1-Vinyl-2-pyrrolidinone is commercially available and was distilled before usage.

To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added $Fe(OTf)_2$ (5.3 mg, 0.015 mmol) and **L2** (4.1 mg, 0.015 mmol). After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (0.8 mL) and MeCN (0.2 mL) were added via a syringe and the mixture was stirred at room temperature for 10 min. To another flame-dried 3-dram vial (vial **B**) equipped with a stir bar was added **2b** (158.4mg, 0.60 mmol). This vial was evacuated and backfilled with N_2 three times and anhydrous CH_2Cl_2 (4.0 mL) was added. Both vials were degassed with brief evacuation and backfilled with N_2 twice. Freshly distilled1-vinyl-2-pyrrolidinone (53.4 μL, 0.5 mmol), $TMSN_3$ (263 μL, 2.0 mmol) were added successively to vial **B** and followed by drop-wise addition of the catalyst solution in vial **A** at room temperature. The reaction was kept at room temperature for 3 h and then quenched with a saturated $NaHCO_3$ solution (0.1 mL) and further diluted with hexanes (5 mL). The mixture was stirred vigorously for additional 10 min and filtered through a short silica gel pad. The filtrate was concentrated *in vacuo*. The residue was subsequently purified through a silica gel flash column (hexanes/EtOAc: from 20:1 to 5:1) as a colorless oil.



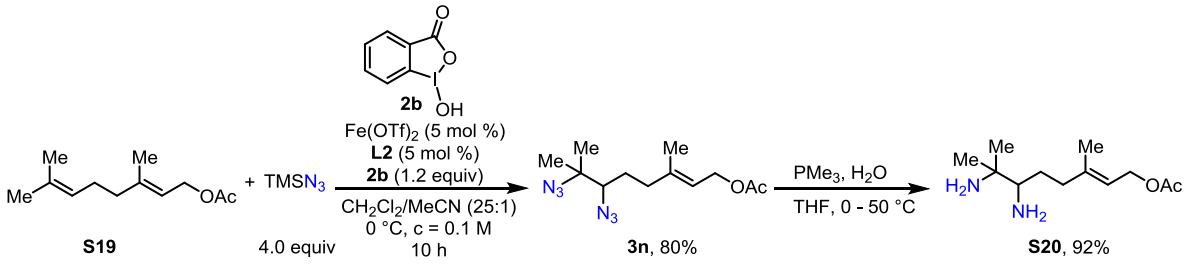
1-(1,2-Diazidoethyl)pyrrolidin-2-one (3m): The titled compound was isolated through a silica gel flash column (hexanes/acetone: from 20:1 to 4:1) as a colorless oil (78.1 mg, 80%

yield). IR ν_{max} (neat)/cm^{-1}: 2932 (m), 2107 (s), 1698 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81 (t, J = 6.6 Hz, 1H), 3.51 (dt, J = 9.2, 7.4 Hz, 1H), 3.46 – 3.31 (m, 3H), 2.47 (td, J = 8.1, 1.6 Hz, 2H), 2.17 – 2.05 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.2, 67.0, 51.4, 42.6, 30.8, 18.4. HRMS (ESI, m/z): calcd for $C_6H_9Cl_3N_7ONa^+$, [M + Na^+], 218.0761, found 218.0757.



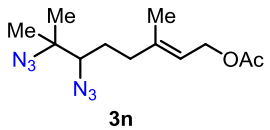
4m

1-(1,2-Diaminoethyl)pyrrolidin-2-one (4m): To a flame-dried sealable 2-dram vial equipped with a stir bar was added diazidation product **3m** (84.1 mg, 0.3 mmol). After the vial was evacuated and backfilled with N_2 three times, THF (6 mL) and H_2O (27 µL, 1.5 mmol) were added via syringes. The solution was cooled to 0 °C under stirring. PMe_3 (0.66 mL, 1M solution in THF) was added dropwise through a syringe. The reaction was then warmed up to room temperature for 15 min and further warmed up to 50 °C for additional 10 h (the reaction was monitored by IR until the absorption of azido groups disappeared). The whole mixture was concentrated *in vacuo* and the residue was then dissolved in Et_2O (5 mL). This solution was added drop-wise to another solution of TsOH·H_2O (142.7 mg, 0.75 mmol) in Et_2O (3 mL). The reaction was kept stirring for 30 min and the white precipitate was collected by filtration, washed with Et_2O (5 mL × 3) and dried *in vacuo*. **4m** was obtained as a white solid (105.3 mg, 72% yield, m.p. 145–146 ˚C). IR ν_{max} (neat)/cm^{-1}: 3020 (s), 2921 (s), 1743 (w), 1699 (s), 1496 (w), 1173 (s), 1123 (s), 1035 (s), 1010 (s), 812 (m), 680 (s); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.29 (br, 6H), 7.52 (d, J = 7.9 Hz, 4H), 7.15 (d, J = 7.8 Hz, 4H), 5.35 (dd, J = 10.5, 3.0 Hz, 1H), 3.40 – 3.30 (m, 3H), 3.22 – 3.11 (m, 1H), 2.38-2.18 (m, 8H), 2.09 – 1.73 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 176.3, 144.9, 138.3, 128.4, 125.6, 55.9, 41.8, 37.5, 30.4, 20.9, 17.4; HRMS (ESI, m/z): calcd for $C_6H_{14}N_3O^+$, [M + H^+], 144.1131, found 144.1125.



Geranyl acetate **S19** was prepared according to a literature procedure.[79]

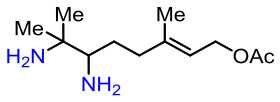
To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added $Fe(OTf)_2$ (8.9 mg, 0.025 mmol) and **L2** (6.8 mg, 0.025 mmol). After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (0.8 mL) and MeCN (0.2 mL) were added via a syringe and the mixture was stirred at room temperature for 10 min. To another flame-dried 3-dram vial (vial **B**) equipped with a stirring bar was added **2b** (158.4 mg, 0.60 mmol) and compound **S19** (98.0 mg, 0.5 mmol). This vial was evacuated and backfilled with N_2 three times and anhydrous CH_2Cl_2 (4.0 mL) was added. Both vials were degassed with brief evacuation and backfilled with N_2 twice. $TMSN_3$ (263 µL, 2.0 mmol) was added successively to vial **B** and followed by drop-wise addition of the catalyst solution in vial **A** at 0 °C. The reaction was kept at 0 °C for 10 h and then quenched with a saturated $NaHCO_3$ solution (0.1 mL) and further diluted with hexanes (5 mL). The mixture was stirred vigorously for additional 10 min and filtered through a short silica gel pad. The filtrate was concentrated *in vacuo*. The residue was subsequently purified through a silica gel flash column (hexanes/Et_2O: from 20:1 to 5:1) as a colorless oil (112.1 mg, 80% yield).



3n

(*E*)-6,7-Diazido-3,7-dimethyloct-2-en-1-yl acetate (**3n**): IR ν_{max} (neat)/cm^{-1}: 2971 (m), 2099 (s), 1740 (m), 1458 (w), 1368 (w), 1259 (s), 1140 (w), 1037 (w); ^1H NMR (400 MHz,

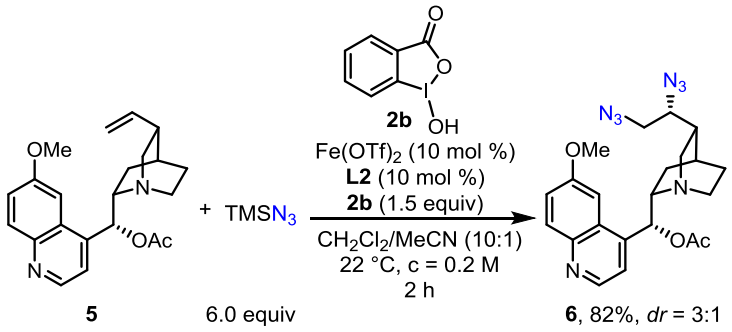
$CDCl_3$): δ 5.40 (t, J = 7.0 Hz, 1H), 4.59 (d, J = 7.0 Hz, 2H), 3.04 (dd, J = 11.1, 2.0 Hz, 1H), 2.37–2.21 (m, 1H), 2.18–2.08 (m, 1H), 2.04 (s, 3H), 1.83–1.73 (m, 1H), 1.71 (s, 3H), 1.56–1.41 (m, 1H), 1.32 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 140.4, 120.1, 70.1, 64.7, 61.3, 36.8, 27.5, 23.0, 22.9, 21.1, 16.4.



S20

(*E*)-6,7-diamino-3,7-dimethyloct-2-en-1-yl acetate (**S20**). To a flame-dried sealable 2-dram vial equipped with a stir bar was added diazidation product **3n** (84.1 mg, 0.3 mmol). After the vial was evacuated and backfilled with N_2 three times, THF (6 mL) and H_2O (27 µL, 1.5 mmol) were added via syringes. The solution was cooled to 0 °C under stirring. PMe_3 (0.66 mL, 1M solution in THF) was added dropwise through a syringe. The reaction was then warmed up to room temperature for 15 min and further warmed up to 50 °C for additional 10 h (the reaction was monitored by IR until the absorption of azido groups disappeared). The whole mixture was concentrated *in vacuo* and diamine **S20** was isolated through a silica gel flash column (CH_2Cl_2/MeOH = 10:1) as a colorless oil (63.0mg, 92% yield). IR ν_{max} (neat)/cm^{-1}: 2964 (brs), 1734 (s), 1568 (m), 1446 (m), 1366 (m), 1223 (s), 1022 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.36 (t, J = 7.1 Hz, 1H), 4.57 (d, J = 7.1 Hz, 2H), 2.34 (dd, J = 10.7, 1.9 Hz, 1H), 2.32–2.21 (m, 1H), 2.09–1.98 (m, 4H), 1.78–1.65 (m, 4H), 1.35 (brs, 4H), 1.20–1.09 (m, 1H), 1.07 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 142.2, 118.6, 61.3, 60.3, 52.5, 37.5, 30.2, 28.2, 25.5, 21.1, 16.5; HRMS (ESI, m/z): calcd for $C_{12}H_{25}N_2O_2^+$, [M + H$^+$], 229.1911, found 229.1914.

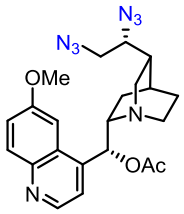
4.2.3 Procedures for the Diazidation of Acetyl Quinine and Glycals



Scheme 66. Procedures for the Diazidation of Acetyl Quinine

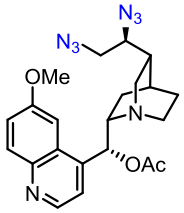
Acetyl quinine **5** was prepared according to a literature procedure.[80]

To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stirring bar were added $Fe(OTf)_2$ (17.7 mg, 0.05 mmol) and **L2** (13.7 mg, 0.05 mmol). After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (0.75 mL) and MeCN (0.25 mL) were added via a syringe and the mixture was stirred at room temperature for 10 min. To another flame-dried 3-dram vial (vial **B**) equipped with a stirring bar were added **2b** (198.0 mg, 0.75 mmol) and **5** (183.3 mg, 0.5 mmol). This vial was evacuated and backfilled with N_2 three times and anhydrous CH_2Cl_2 (1.5 mL) was added. Both vials were degassed with brief evacuation and backfilled with N_2 twice. $TMSN_3$ (395 μl, 3.0 mmol) was added to vial **B** and followed by drop-wise addition of the catalyst solution in vial **A** at room temperature. The reaction was kept at room temperature for 2 h and then quenched with saturated $NaHCO_3$ solution (0.1 mL), and further diluted with hexanes (5 mL). The mixture was stirred vigorously for 10 min and filtered through a short silica gel pad. The filtrate was concentrated *in vacuo*. The residue was subsequently purified through a silica gel flash column (CH_2Cl_2/MeOH: from 50:1 to 20:1) as white foam (184.7 mg, 82% yield, *dr* = 3:1).



6a

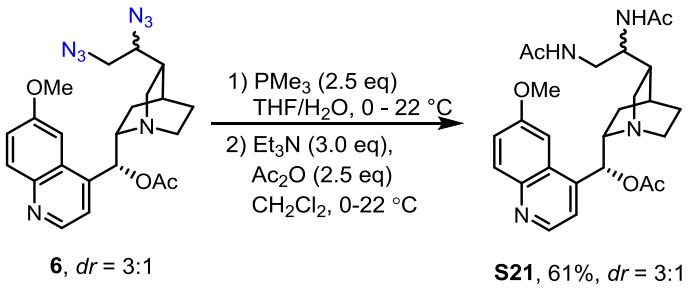
(*R*)-((1*S*,2*S*,4*S*,5*R*)-5-((*R*)-1,2-diazidoethyl)quinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl acetate (**6a**): IR ν_{max} (neat)/cm^{-1}: 3364 (w), 2928 (m), 2871 (w), 2102 (s), 1744 (s), 1622 (m), 1508 (m), 1229 (s), 1030 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (d, J = 4.5 Hz, 1H), 8.02 (d, J = 9.0 Hz, 1H), 7.44–7.36 (m, 2H), 7.34 (d, J = 4.5 Hz, 1H), 6.49 (d, J = 7.1 Hz, 1H), 3.96 (s, 3H), 3.57 (dd, J = 15.6, 6.4 Hz, 1H), 3.44–3.31 (m, 3H), 3.15–3.06 (m, 1H), 3.02 (dd, J = 14.1, 9.9 Hz, 1H), 2.72–2.58 (m, 2H), 2.13 (s, 3H), 1.82 (s, 1H), 1.78–1.64 (m, 3H), 1.63–1.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 158.4, 147.8, 145.2, 143.6, 132.3, 127.3, 122.1, 119.1, 101.7, 73.9, 65.8, 59.3, 56.0, 55.2, 54.4, 42.6, 37.4, 28.4, 24.6, 24.5, 21.4.



6b

(*R*)-((1*S*,2*S*,4*S*,5*R*)-5-((*S*)-1,2-diazidoethyl)quinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl acetate (**6b**): IR ν_{max} (neat)/cm^{-1}: 3364 (w), 2929 (m), 2103 (s), 1744 (s), 1620 (m), 1508 (m), 1230 (s), 1029 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (d, J = 4.5 Hz, 1H), 8.03 (d, J = 9.1 Hz, 1H), 7.42 (d, J = 2.5 Hz, 1H), 7.38 (dd, J = 9.1, 2.6 Hz, 1H), 7.34 (d, J = 4.5 Hz, 1H), 6.48 (d, J = 7.2 Hz, 1H), 3.96 (s, 3H), 3.50–3.39 (m, 1H), 3.35–3.19 (m, 3H), 3.14–3.04 (m, 1H), 2.99 (dd, J = 13.8, 10.0 Hz, 1H), 2.68–2.55 (m, 1H), 2.29 (dd, J = 13.6, 3.3 Hz, 1H), 2.14 (s, 3H), 2.15–2.09 (m, 1H), 1.85–1.72 (m, 2H), 1.69–1.59 (m, 2H), 1.56–1.45 (m, 1H); ^{13}C NMR

(100 MHz, $CDCl_3$): δ 170.4, 158.3, 147.8, 145.2, 143.7, 132.3, 127.3, 122.0, 119.2, 101.9, 73.9, 65.3, 59.9, 56.0, 55.1, 53.7, 42.6, 37.7, 28.0, 24.5, 23.8, 21.4.



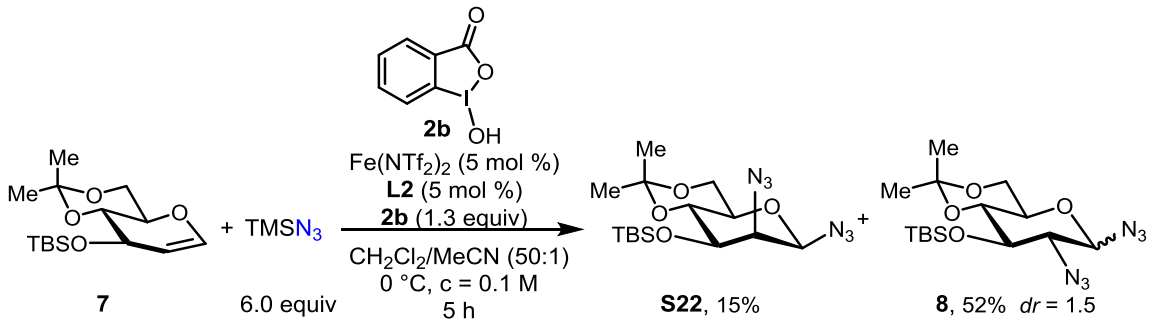
6, *dr* = 3:1

S21, 61%, *dr* = 3:1

Scheme 67. Reduction of Acetyl Quinine

To a flame-dried sealable 2-dram vial equipped with a stir bar was added diazidation product **6** (135.2 mg, 0.3 mmol, *dr* = 3:1). After the vial was evacuated and backfilled with N_2 three times, THF (6 mL) and H_2O (27 μL, 1.5 mmol) were added via syringes. The solution was cooled to 0 °C under stirring. PMe_3 (0.75 mL, 1M solution in THF) was added drop-wise via a syringe. The reaction was then warmed up to room temperature and kept stirring for additional 4 h (the reaction was monitored by IR until the absorption of azido groups disappeared). The whole mixture was then concentrated and dried *in vacuo*. The crude product was dissolved in anhydrous CH_2Cl_2 (3 mL) under N_2. This solution was cooled to 0 °C and Et_3N (125 μL, 0.9 mmol) was then added followed by drop-wise addition of Ac_2O (71 μL, 0.75 mmol). The reaction was gradually warmed up to room temperature, stirred for 4 h and quenched with a saturated $NaHCO_3$ solution (2 mL). After the organic layer was separated, the aqueous phase was extracted with CH_2Cl_2 (5 mL × 4). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was then purified through a silica gel flash column (from CH_2Cl_2/MeOH 10:1 to CH_2Cl_2/MeOH (buffered with 5% NH_4OH aq.) 2:1) to afford the protected product **S21** as a viscous oil (88.3 mg, 61% yield, *dr* = 3:1). IR ν_{max} (neat)/cm^{-1}: 3270(w), 2937 (m), 1742 (m), 1652 (s) 1228 (s), 1027 (m), 912 (m); ^{1}H NMR (400

MHz, $CDCl_3$): δ 8.73 (d, J = 4.6 Hz, 1H), 8.00 (d, J = 9.2 Hz, 1H, minor), 7.99 (d, J = 9.2 Hz, 1H), 7.44 (d, J = 2.7 Hz, 1H, minor), 7.43 (d, J = 2.6 Hz, 1H), 7.39–7.32 (m, 2H), 6.48 (d, J = 8.0 Hz, 1H), 6.44 (d, J = 7.7 Hz, 1H, minor), 6.18–6.09 (m, 1H), 5.96 (d, J = 9.0 Hz, 1H, minor), 5.78 (d, J = 9.0 Hz, 1H), 4.05 (ddd, J = 13.0, 9.7, 3.8 Hz, 1H), 3.96 (s, 3H), 3.94–3.88 (m, 1H, minor), 3.47 (q, J = 8.1 Hz, 1H), 3.34 (ddd, J = 14.1, 9.7, 7.1 Hz, 1H), 3.24 (dt, J = 13.8, 3.8 Hz, 1H), 3.13–3.00 (m, 1H), 2.85 (dd, J = 13.9, 9.8 Hz, 1H), 2.62–2.47 (m, 2H), 2.36 (dd, J = 13.7, 4.1 Hz, 1H, minor), 2.10 (s, 3H), 1.95 (s, 3H), 1.94 (s, 3H), 1.92–1.82 (m, 2H), 1.78–1.68 (m, 1H), 1.58–1.37 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 171.4 (minor), 171.2, 170.8 (minor), 170.19, 170.17 (minor), 158.0, 157.95 (minor), 147.42, 147.39 (minor), 144.72 (minor), 144.66, 143.6 (minor), 143.5, 131.7 (minor), 131.6, 127.3, 127.1 (minor), 121.9, 121.8 (minor), 119.1, 101.7 (minor), 101.5, 73.6 (minor), 73.3, 59.5 (minor), 58.6, 55.7 (minor), 55.65, 54.5, 52.6, 52.5 (minor), 43.8, 42.9 (minor), 42.2, 42.1 (minor), 38.4 (minor), 38.3, 28.0 (minor), 27.9, 24.6, 24.5 (minor), 23.9, 23.4 (minor), 23.3 (minor), 23.2, 23.14, 23.10 (minor), 21.1; HRMS (ESI, m/z): calcd for $C_{26}H_{35}N_4O_5^+$, [M + H^+], 483.2602, found 483.2586.



Scheme 68. Procedures for the Diazidation of Glycals

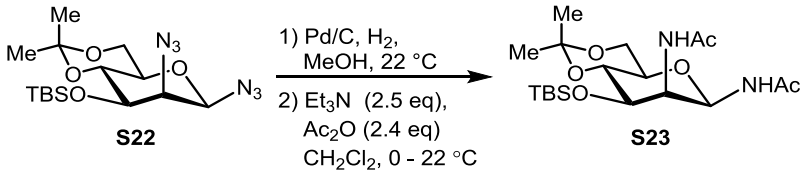
Glycal **7** was prepared according to a literature procedure.[81]

To a flame-dried sealable 3-dram vial equipped with a stir bar were added $Fe(NTf_2)_2$ (153.7 mg, 0.25 mmol) and **L2** (68.3 mg, 0.25 mmol). After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (4 mL) and MeCN (1 mL) were added via a

syringe and the mixture was stirred at room temperature for 10 min. To a flame-dried round-bottom flask (100 mL) equipped with a stirring bar were added **2b** (1.72 mg, 6.5 mmol) and compound **7** (1.50 g, 5 mmol). The flask was evacuated and backfilled with N_2 three times and anhydrous CH_2Cl_2 (45 mL) was added. Both the vial and the flask were degassed with brief evacuation and backfilled with N_2 twice. After the flask was cooled to 0 °C, $TMSN_3$ (3.95 ml, 30 mmol) was added into it and followed by drop-wise addition of the catalyst solution in the vial. The reaction was kept at 0 °C for 5 h and then quenched with saturated $NaHCO_3$ solution (1 mL). The mixture was transferred to an Erlenmeyer flask (200 mL) and diluted with hexanes (100 mL). The mixture was stirred vigorously for 10 min and filtered through a short silica gel pad. The filtrate was concentrated *in vacuo* and the residue was subsequently purified through a silica gel flash column (hexanes/Et_2O: from 60:1 to 25:1). Three diastereomers were isolated as colorless oil (288 mg, 15% yield for **S22**, 385 mg, 20% yield for **8a** and 615 mg, 32% yield for **8b**).

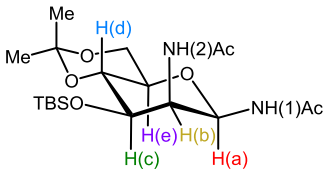
S22

***tert*-Butyl(((4*aR*,6*S*,7*S*,8*R*,8*aR*)-6,7-diazido-2,2-dimethylhexahydropyrano[3,2-d][1,3]dioxin -8-yl)oxy)dimethylsilane** (**S22**): IR ν_{max} (neat)/cm^{-1}: 2927 (w), 2856 (w), 2105 (s), 1473 (s), 1374 (w), 1247 (m), 1122 (m), 1096 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.26 (d, J = 1.4 Hz, 1H), 4.04 (dd, J = 9.4, 3.8 Hz, 1H), 3.89 (t, J = 9.4 Hz, 1H), 3.86 (dd, J = 10.4, 5.1 Hz, 1H), 3.79 (t, J = 10.2 Hz, 1H), 3.75–3.69 (m, 1H), 3.68 (dd, J = 3.7, 1.4 Hz, 1H), 1.51 (s, 3H), 1.40 (s, 3H), 0.90 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 99.9, 89.2, 71.1, 70.3, 67.0, 64.5, 61.9, 29.1, 25.7, 19.2, 18.3, -4.4, -4.9.



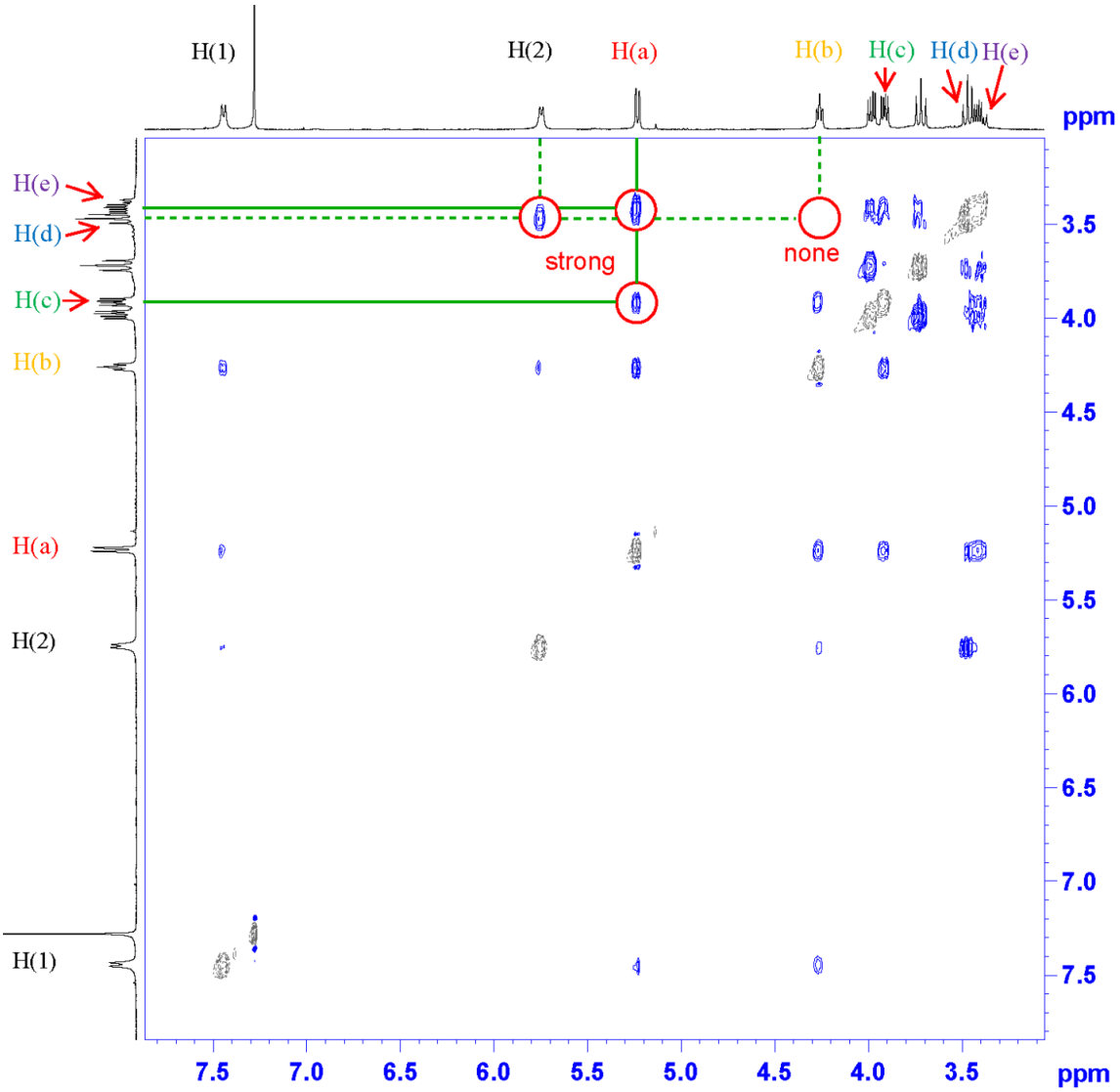
***N*,*N*'-((4*aR*,6*R*,7*S*,8*R*,8*aR*)-8-((*tert*-Butyldimethylsilyl)oxy)-2,2-dimethylhexahydropyrano [3,2-d][1,3]dioxine-6,7-diyl)diacetamide** (**S23**): To a 3-dram vial equipped with a stir bar was added Pd/C (3.4 mg, 10 wt%). After the vial was evacuated and backfilled twice with N_2, a solution of diazidation product **S22** (76.9 mg, 0.2 mmol, dissolved in 3 mL MeOH) was added to the vial. The mixture was degassed by brief evacuation and backfilled twice with N_2 and then three times with H_2. The reaction was vigorously stirred under H_2 at room temperature until the reduction completed (the reaction was monitored by IR until the absorption of azido groups disappeared). The solution was filtered through Celite, washed with MeOH (3 mL). The filtrate was concentrated *in vacuo* and the residue was re-dissolved in CH_2Cl_2 (3 mL). This solution was cooled to 0 °C and Et_3N (68 μL, 0.5 mmol) was then added followed by drop-wise addition of Ac_2O (46 μL, 0.48 mmol). The reaction was gradually warmed up to room temperature, stirred for 4 h and quenched with saturated $NaHCO_3$ solution (1 mL). After the organic layer was separated, the aqueous phase was extracted with CH_2Cl_2 (5 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified through a silica gel flash column (hexanes/acetone from 4:1 to 2:1) to afford **S23** as colorless oil (63.3 mg, 76% yield). IR ν_{max} (neat)/cm^{-1}: 3281 (w), 2932 (w), 1661 (s), 1540 (m), 1371 (m), 1257 (m), 1090 (s); ^1H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, J = 7.7 Hz, 1H), 5.73 (d, J = 6.6 Hz, 1H), 5.21 (dd, J = 7.7, 1.4 Hz, 1H), 4.24 (t, J = 6.0 Hz, 1H), 3.96 (dd, J = 10.7, 5.0 Hz, 1H), 3.89 (dd, J = 9.1, 5.1 Hz, 1H), 3.70 (t, J = 10.5, 1H), 3.45 (t, J = 9.4 Hz, 1H), 3.42–3.35 (m, 1H), 2.14 (s, 3H), 2.00 (s, 3H), 1.48 (s, 3H), 1.40 (s, 3H), 0.86 (s,

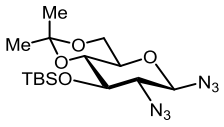
9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 170.4, 99.9, 79.1, 72.0, 70.5, 70.0, 62.0, 55.1, 29.0, 25.5, 23.6, 23.4, 19.3, 18.1, -4.6, -5.2; HRMS (ESI, m/z): calcd for $C_{19}H_{37}N_2O_6Si^+$, [M + H^+], 417.2415, found 417.2425.



S23

The stereochemistry of **S23** was determined through *NOE* analysis. Strong *NOEs* were observed between H(a) and H(c), and H(a) and H(e). Additionally, a significant *NOE* was observed between H(d) and H(2).

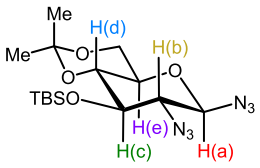




8a

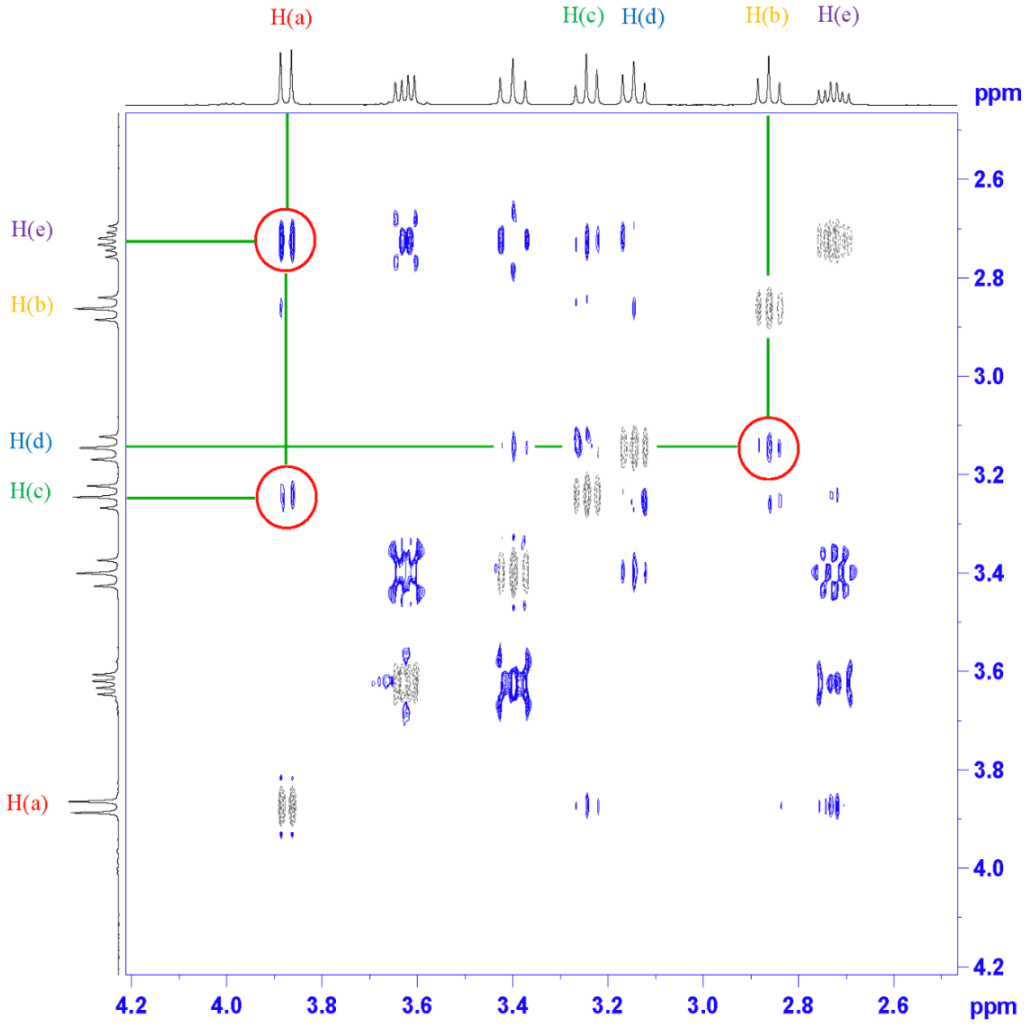
***tert*-Butyl(((4a*R*,6*R*,7*R*,8*R*,8a*R*)-6,7-diazido-2,2-dimethylhexahydropyrano[3,2-d][1,3]dioxin -8-yl)oxy)dimethylsilane** (**8a**): IR ν_{max} (neat)/cm^{-1}: 2108 (s), 1371 (w), 1248 (m), 1094 (s); ^{1}H NMR (400 MHz, C_6D_6): δ 3.87 (d, J = 9.1 Hz, 1H), 3.63 (dd, J = 10.7, 5.3 Hz, 1H), 3.40 (t, J = 10.5 Hz, 1H), 3.24 (t, J = 8.9 Hz, 1H), 3.15 (t, J = 9.2 Hz, 1H), 2.86 (t, J = 9.0 Hz,

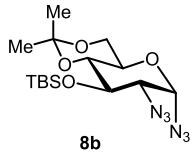
1H), 2.73 (td, *J* = 9.9, 5.3 Hz, 1H), 1.34 (s, 3H), 1.13 (s, 3H), 1.03 (s, 9H), 0.21 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ 99.2, 89.2, 73.7, 73.3, 69.1, 68.2, 61.4, 28.7, 25.6, 18.4, 18.1, -4.5, -5.1.



8a

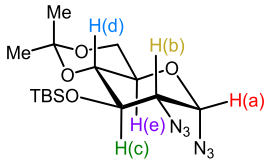
The stereochemistry of **8a** was determined through *NOE* analysis. Strong *NOEs* were observed between H(a) and H(c), and H(a) and H(e). Additionally, a significant *NOE* was observed between H(b) and H(d).





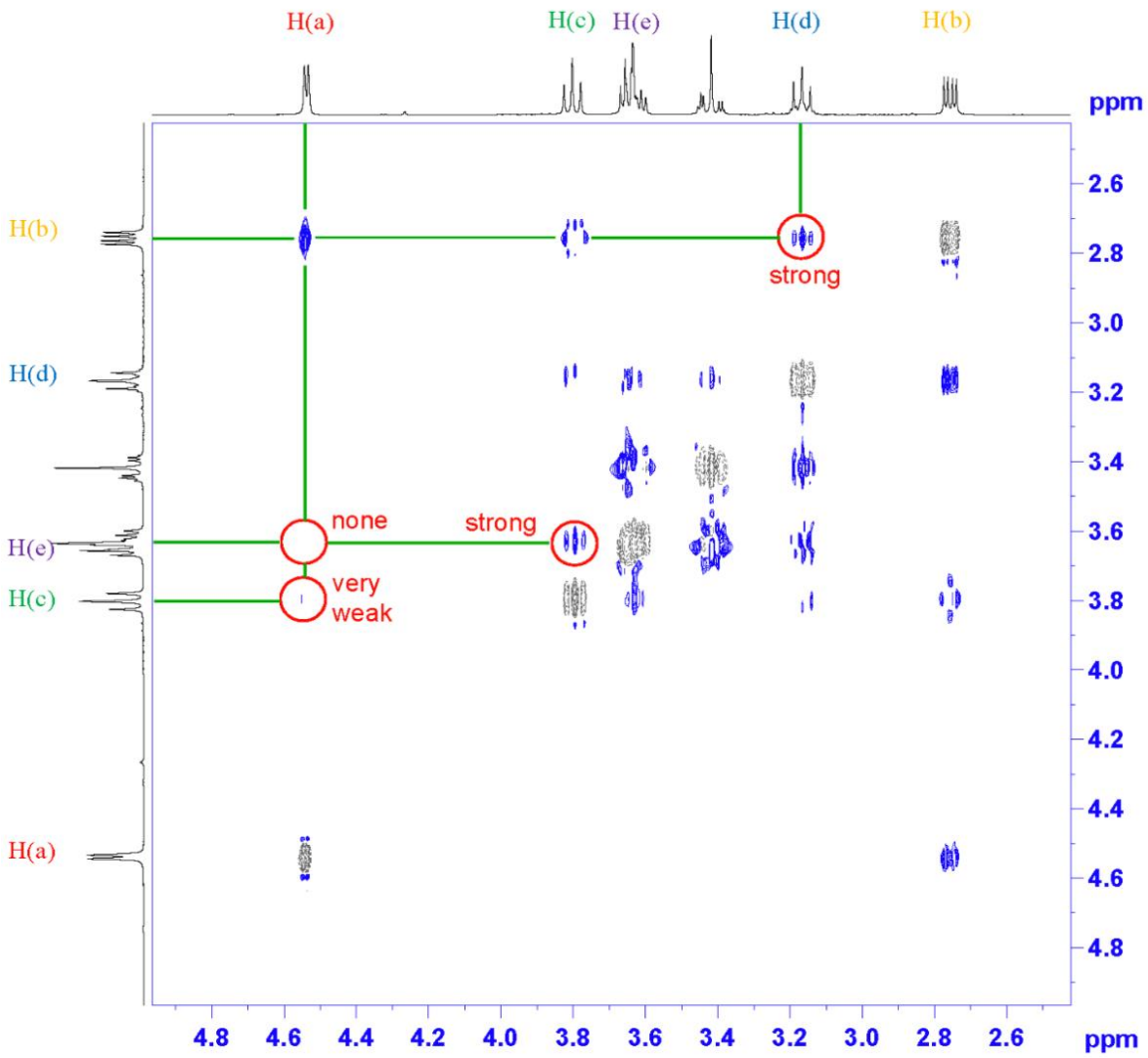
8b

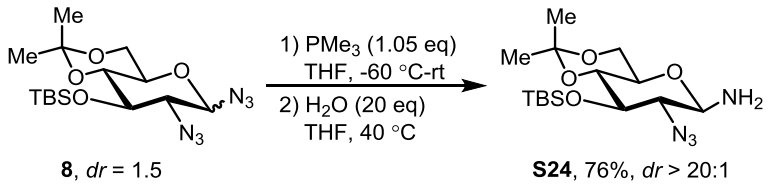
***tert*-Butyl(((4a*R*,6*S*,7*R*,8*R*,8a*R*)-6,7-diazido-2,2-dimethylhexahydropyrano[3,2-d][1,3]dioxin -8-yl)oxy)dimethylsilane** (**8b**): IR ν_{max} (neat)/cm^{-1}: 2106 (s), 1249 (m), 1130 (s), 1097 (s); ^{1}H NMR (400 MHz, C_6D_6): δ 4.54 (d, J = 4.3 Hz, 1H), 3.80 (t, J = 9.1 Hz, 1H), 3.69–3.58 (m, 2H), 3.47–3.36 (m, 1H), 3.21–3.11 (m, 1H), 2.76 (dd, J = 9.5, 4.3 Hz, 1H), 1.37 (s, 3H), 1.18 (s, 3H), 1.03 (s, 9H), 0.22 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ 99.6, 88.9, 74.2, 70.6, 65.7, 64.8, 61.8, 28.8, 25.6, 18.5, 18.1, -4.3, -5.6.



8b

The stereochemistry of **8b** was determined through *NOE* analysis. No *NOE* was observed between H(a) and H(c), and H(a) and H(e). However, a significant *NOE* was observed between H(b) and H(d).

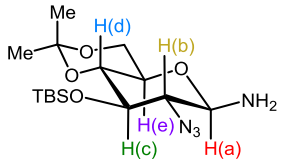




8, *dr* = 1.5 **S24**, 76%, *dr* > 20:1

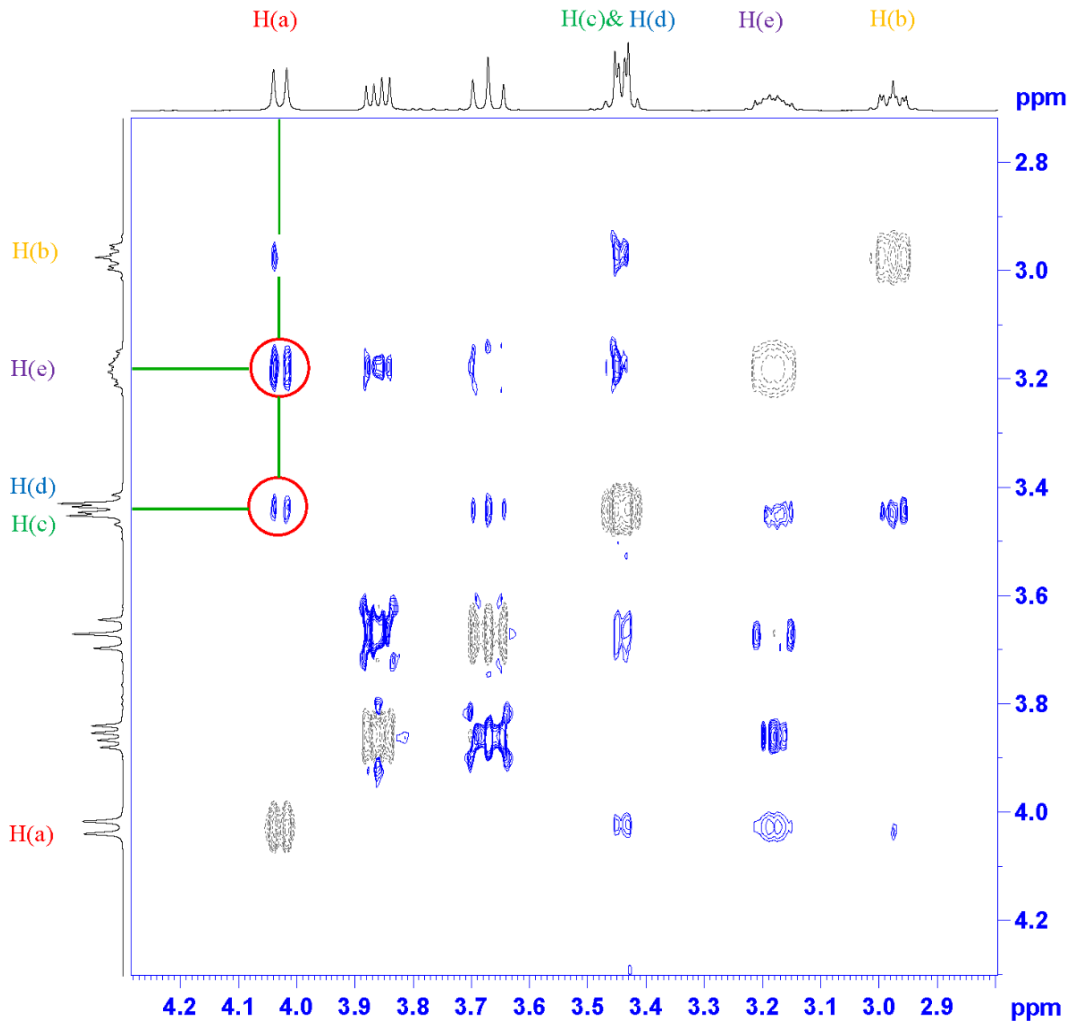
(4*aR*,6*R*,7*R*,8*R*,8*aR*)-7-Azido-8-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethylhexahydropyrano [3,2-d][1,3]dioxin-6-amine (**S24**). To a flame-dried sealable 2-dram vial equipped with a stir bar was added a mixture of **8b** and **8a** (153.8 mg, 0.4 mmol, *dr* = 1.5:1). The vial was evacuated and backfilled with N_2 three times and THF (4 mL) was added

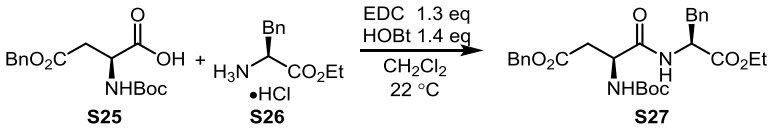
through a syringe. After the solution was cooled to -60 °C under stirring, PMe_3 (0.42 mL, 1M solution in THF) was added drop-wise through a syringe and the reaction was kept at -60 °C for 4 h and warmed up gradually to room temperature. Subsequently, water (144 uL) was added, the reaction mixture was further warmed up to 40 °C and stirred for additional 5 h. The whole mixture was concentrated *in vacuo* and **S24** was isolated through a silica gel flash column (hexanes/EtOAc: from 10:1 to 2:1) as colorless oil (109 mg, 76% yield, *dr* > 20:1). IR ν_{max} (neat)/cm^{-1}: 2106 (s), 1370 w), 1264 (m), 1128 (m), 1090 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.04 (d, J = 8.7 Hz, 1H), 3.87 (dd, J = 10.7, 5.4 Hz, 1H), 3.68 (t, J = 10.5 Hz, 1H), 3.51–3.41 (m, 2H), 3.24–3.13 (m, 1H), 3.03–2.93 (m, 1H), 1.99 (s, 2H), 1.46 (s, 3H), 1.39 (s, 3H), 0.91 (s, 9H), 0.13 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 99.4, 85.9, 74.3, 74.1, 70.5, 68.4, 62.2, 29.0, 25.8, 18.9, 18.3, -4.3, -4.9; HRMS (ESI, m/z): calcd for $C_{15}H_{31}N_4O_4Si^+$, [M + H^+], 359.2109, found 359.2116.



S24

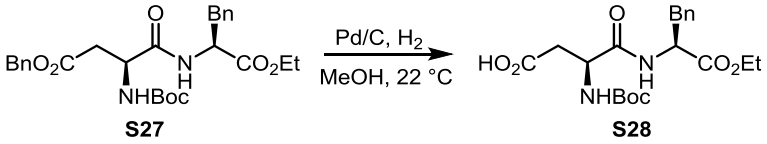
The stereochemistry of **S24** was determined through *NOE* analysis. Strong *NOEs* were observed between H(a) and H(c), and H(a) and H(e).





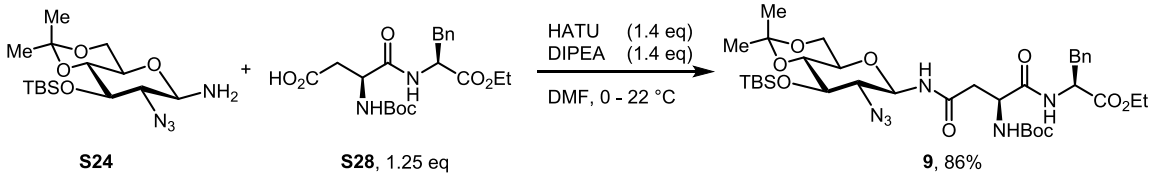
Boc-Asp(OBz)-Phe-OEt (**S27**): To a stirred solution of *L*-aspartic acid *β*-benzyl ester **S25** (647 mg, 2.0 mmol) and *L*-phenylalanine ethyl ester hydrochloride **S26** (466 mg, 2.6 mmol) in DCM were added 1-hydroxybenzotriazole hydrate (HOBt) (505 mg, 2.8 mmol) and 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride (EDC) (498 mg, 2.6 mmol) at 0 °C. The mixture was stirred at room temperature for 18 h. After the solvent was removed *in vacuo*, the residue was dissolved in EtOAc and washed successively with 5% citric acid, 5% sodium

bicarbonate and brine (5 mL each). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified through a silica gel flash column (hexane/EtOAc = 4:1) to give amide **S27** as colorless oil (748 mg, 75% yield). IR ν_{max} (neat)/cm^{-1}: 3335 (w), 2979 (w), 1734 (s), 1674 (s), 1497 (s), 1367 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.32 (m, 5H), 7.31–7.27 (m, 2H), 7.26–7.21 (m, 1H), 7.18–7.12 (m, 2H), 6.95 (d, J = 6.8 Hz, 1H), 5.64 (d, J = 8.0 Hz, 1H), 5.21–5.05 (m, 2H), 4.78 (dd, J = 13.5, 6.0 Hz, 1H), 4.54 (s, 1H), 4.13 (q, J = 7.1 Hz, 2H), 3.09 (d, J = 5.9 Hz, 2H), 3.05 (dd, J =17.2, 2.7 Hz, 1H), 2.71 (dd, J = 17.2, 6.0 Hz, 1H), 1.42 (s, 9H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 170.9, 170.3, 155.4, 135.8, 135.4, 129.4, 128.6, 128.5, 128.4, 128.3, 127.1, 80.5, 66.9, 61.5, 53.5, 50.5, 37.9, 36.1, 28.3, 14.1; HRMS (ESI, m/z): calcd for $C_{27}H_{35}N_2O_7^+$, [M + H^+], 499.2439, found 499.2449.



Boc-Asp-Phe-OEt (**S28**): To a round bottom flask equipped with a stirring bar was added Pd/C (50 mg, 10 wt%). After the flask was evacuated and backfilled twice with N_2, a solution of dipeptide **S27** (499 mg, 1.0 mmol, dissolved in 10 mL methanol) and MeOH (10 mL) was added. The mixture was degassed by brief evacuation and backfilled twice with N_2 and then three times with H_2. The reaction was then vigorously stirred under H_2 at room temperature for 2 h (the reaction was monitored by TLC until **S27** was fully consumed). The reaction mixture was filtered through Celite. The filtrate was concentrated *in vacuo*, dissolved in minimum amount of EtOH (ca. 0.5 mL), and then diluted with Et_2O (10 ml). The resulting white precipitate was collected by filtration and washed with Et_2O (5 ml × 3) to give acid **S28** as a white solid (372 mg, 91% yield, m.p. 128–129 °C). IR ν_{max} (neat)/cm^{-1}: 3316 (w), 2977 (m), 1711 (s) 1664 (s), 1517 (m), 1497 (m), 1368 (m), 1161 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (brs, 1H), 7.34–7.18

(m, 3H), 7.13 (d, *J* = 6.7 Hz, 2H), 7.02 (s, 1H), 5.62 (s, 1H), 4.78 (dd, *J* = 13.5, 6.1 Hz, 1H), 4.49 (s, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.08 (d, *J* = 5.8 Hz, 2H), 2.95 (dd, *J* = 16.8, 4.6 Hz, 1H), 2.71 (dd, *J* = 16.8, 5.9 Hz, 1H), 1.42 (s, 9H), 1.19 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.4, 171.1, 170.8, 155.6, 135.8, 129.4, 128.5, 127.1, 80.7, 61.6, 53.6, 50.4, 37.8, 36.0, 28.2, 14.0; HRMS (ESI, m/z): calcd for $C_{20}H_{29}N_2O_7^+$, [M + H^+], 409.1969, found 409.1979.

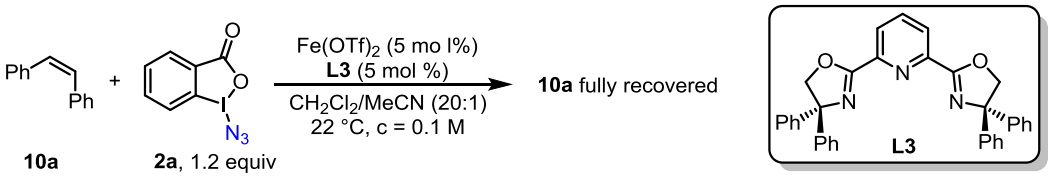


S24 **S28**, 1.25 eq **9**, 86%

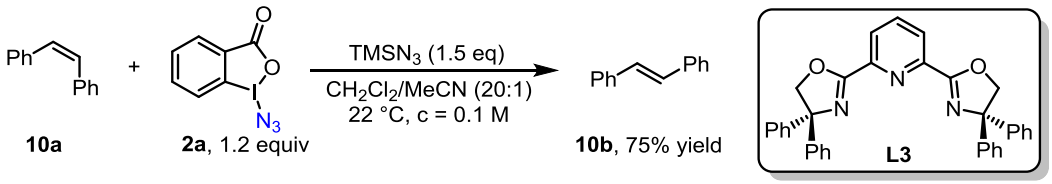
Ethyl *N*^{4}-((4*aR*,6*R*,7*R*,8*R*,8*aR*)-7-azido-8-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethylhexahy-dropyrano[3,2-d][1,3]dioxin-6-yl)-*N*^{2}-(tert-butoxycarbonyl)-*L*-asparaginyl-*L*-phenylalaninate (**9**). To a flame-dried sealable 2-dram vial charged with a stir bar was added dipeptide **S28** (102.1 mg, 0.25 mmol). After the vial was evacuated and backfilled with N_2 three times, anhydrous DMF (2 mL) was added via a syringe. HATU and DIPEA were added to the reaction successively at 0 °C and it was stirred for 10 min before a DMF solution of amine **S24** (71.7 mg, 0.2 mmol, 1 mL) was added. The reaction was then warmed up to room temperature and stirred for 16 h. After quenching with saturated $NaHCO_3$ solution (2 mL), the mixture was further diluted with water (20 mL) and extracted with EtOAc (10 mL × 4). The combined organic layers were concentrated *in vacuo* and subsequently purified through a silica gel flash column (hexanes/EtOAC: from 10:1 to 1:1). **9** was isolated as white foam (128.8 mg, 86% yield). IR ν_{max} (neat)/cm^{-1}: 3311 (w), 3260 (w), 3068 (w), 2110 (s), 1739 (m), 1653 (s), 1545 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 7.8 Hz, 1H), 7.35–7.21 (m, 3H), 7.20–7.10 (m, 3H), 6.01 (d, *J* = 6.8 Hz, 1H), 5.00 (t, *J* = 9.4 Hz, 1H), 4.74 (dd, *J* = 13.5, 6.0 Hz, 1H), 4.50 (d, *J* = 5.7 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.86 (dd, *J* = 10.7, 5.3 Hz, 1H), 3.65 (t, *J* = 10.5 Hz, 1H), 3.56 (t, *J* = 8.9 Hz, 1H), 3.45 (t, *J* = 9.2 Hz, 1H), 3.34–3.20 (m, 2H), 3.16–3.02 (m, 2H), 2.85 (dd, *J* =

15.2, 3.0 Hz, 1H), 2.64 (dd, *J* = 15.4, 5.7 Hz, 1H), 1.43 (s, 3H), 1.41 (s, 9H), 1.38 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H), 0.90 (s, 9H), 0.13 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 171.2, 171.0, 155.8, 135.7, 129.4, 128.6, 127.1, 99.5, 80.5, 78.8, 74.6, 73.7, 69.3, 67.7, 61.9, 61.5, 53.7, 51.2, 37.8, 37.6, 28.9, 28.3, 25.7, 18.9, 18.2, 14.1, -4.3, -4.9; HRMS (ESI, m/z): calcd for $C_{35}H_{57}N_6O_{10}Si^+$, [M + H^+], 749.3900, found 749.3915.

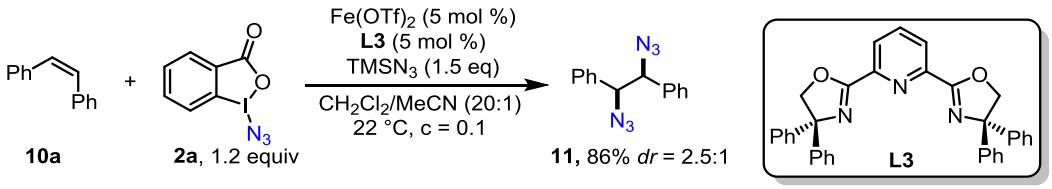
4.2.4 Mechanistic Investigation of the Iron-Catalyzed Olefin Diazidation



To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added $Fe(OTf_2)_2$ (3.5 mg, 0.01 mmol) and **L3** (5.2 mg, 0.01 mmol). After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (0.4 mL) and MeCN (0.1 mL) were added via a syringe and the mixture was stirred at room temperature for 10 min. To another flame-dried 3-dram vial (vial **B**) equipped with a stirring bar was added **2a** (69.4 mg, 0.24 mmol). This vial was evacuated and backfilled with N_2 three times and anhydrous CH_2Cl_2 (1.5 mL) was added. Both vials were degassed with brief evacuation and backfilled with N_2 twice. *cis*-Stilbene **10a** (36 µL, 0.2 mmol) was added via a syringe to vial **B** and followed by drop-wise addition of the catalyst solution in vial **A**, the reaction was kept at room temperature for 2 h and then quenched with saturated $NaHCO_3$ solution (0.1 mL), and further diluted with hexanes (3 mL). The mixture was stirred vigorously for 10 min and filtered through a short silica gel pad. The filtrate was concentrated *in vacuo* and the crude product was analyzed by ^{1}H NMR with trimethoxybenzene as an internal standard. *cis*-Stilbene was almost fully recovered (>95% NMR yield).

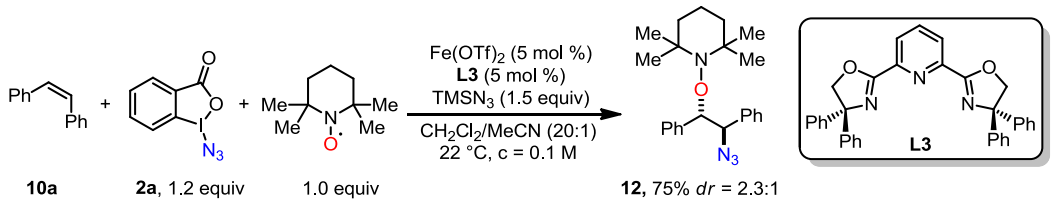


To a flame-dried sealable 3-dram vial equipped with a stir bar was added **2a** (69.4 mg, 0.24 mmol). After this vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (1.9 mL) and MeCN (0.1) were added. *cis*-Stilbene **10a** (36 µL, 0.2 mmol) and $TMSN_3$ (40 µl, 0.3 mmol) were then added into the reaction successively via syringes at room temperature. The reaction was kept stirring at room temperature for 2 h and then quenched with a saturated $NaHCO_3$ solution (0.1 mL), and further diluted with hexanes (3 mL). The mixture was stirred vigorously for 10 min and filtered through a short silica gel pad. The filtrate was concentrated *in vacuo* and the crude product was analyzed by ^1H NMR with trimethoxybenzene as an internal standard. *cis*-Stilbene **10a** was fully converted to *trans*-stilbene **10b** (75% NMR yield).



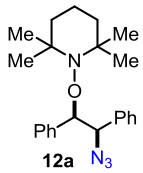
To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added $Fe(OTf_2)_2$ (3.5 mg, 0.01 mmol) and **L3** (5.2mg, 0.01 mmol). After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (0.4 mL) and MeCN (0.1 mL) were added via a syringe and the mixture was stirred at room temperature for 10 min. To another flame-dried 3-dram vial (vial **B**) equipped with a stirring bar was added **2a** (69.4 mg, 0.24 mmol). This vial was evacuated and backfilled with N_2 three times and anhydrous CH_2Cl_2 (1.5 mL) was added. Both vials were degassed with brief evacuation and backfilled with N_2 twice. *cis*-Stilbene **10a** (36 µL, 0.2 mmol) and $TMSN_3$ (40 µl, 0.3 mmol) were added successively to vial **B** and followed by

drop-wise addition of the catalyst solution in vial **A** at room temperature, the reaction was kept at room temperature for 2 h and then quenched with saturated $NaHCO_3$ solution (0.1 mL), and further diluted with hexanes (3 mL). The mixture was stirred vigorously for 10 min and filtered through a short silica gel pad. The filtrate was concentrated *in vacuo* and the crude product was analyzed by ^1H NMR with trimethoxybenzene as an internal standard (86% yield, and *dr* = 2.5).

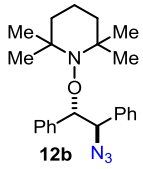


10a **2a**, 1.2 equiv 1.0 equiv **12**, 75% *dr* = 2.3:1

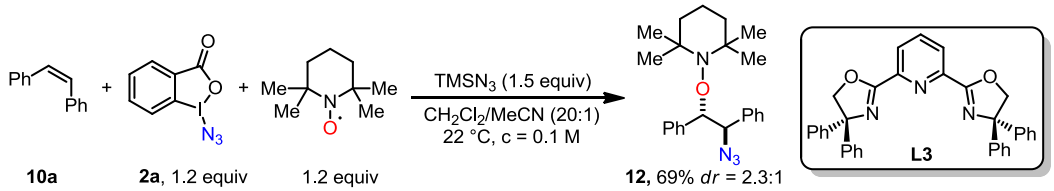
To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added $Fe(OTf_2)_2$ (3.5 mg, 0.01 mmol) and **L3** (5.2 mg, 0.01 mmol). After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (0.4 mL) and MeCN (0.1 mL) were added via a syringe and the mixture was stirred at room temperature for 10 min. To another flame-dried 3-dram vial (vial **B**) equipped with a stirring bar were added **2a** (69.4 mg, 0.24 mmol) and TEMPO (31.3 mg, 0.2 mmol). This vial was evacuated and backfilled with N_2 three times and anhydrous CH_2Cl_2 (1.5 mL) was added. Both vials were degassed with brief evacuation and backfilled with N_2 twice. *cis*-Stilbene **10a** (36 µL, 0.2 mmol) and $TMSN_3$ (40 µl, 0.3 mmol) were added to vial **B** successively and followed by drop-wise addition of the catalyst solution in vial **A**. The reaction was kept at room temperature for 2 h and then quenched with saturated $NaHCO_3$ solution (0.1 mL), and further diluted with hexanes (3 mL). The mixture was stirred vigorously for 10 min and filtered through a short silica gel pad. The filtrate was concentrated *in vacuo* and the crude product was analyzed by ^1H NMR with trimethoxybenzene as an internal standard. The azido-oxygenation product **12** was identified (75% yield, *dr* = 2.3).[82]



(±)-1-((1*R*,2*S*)-2-Azido-1,2-diphenylethoxy)-2,2,6,6-tetramethylpiperidine (**12a**): IR ν_{max} (neat)/cm^{-1}: 2933 (s), 2100 (s), 1455 (m), 1258 (m), 1133 (w), 757 (w), 698 (m); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26–7.14 (m, 6H), 7.10–7.01 (m, 4H), 5.18 (d, J = 8.0 Hz, 1H), 5.07 (d, J = 8.0 Hz, 1H), 1.91–0.88 (m, 16H), 0.65–0.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9, 136.8, 129.7, 128.14, 128.08, 127.9, 127.8, 127.4, 89.2, 69.3, 61.1, 59.6, 41.0, 34.8, 34.1, 20.7, 17.2.

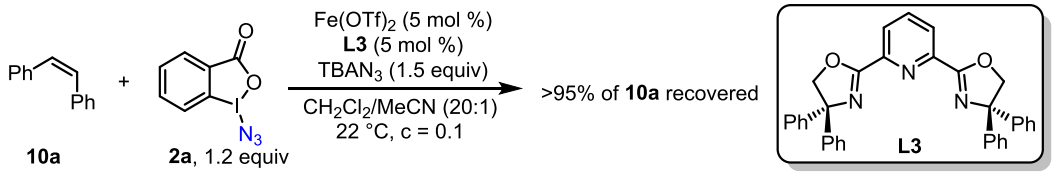


(±)1-((1*S*,2*S*)-2-Azido-1,2-diphenylethoxy)-2,2,6,6-tetramethylpiperidine (**12b**): IR ν_{max} (neat)/cm^{-1}: 2932 (s), 2100 (s), 1452 (m), 1361 (w), 1133 (w), 1025 (m), 709 (s); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25–7.12 (m, 6H), 7.00–6.88 (m, 4H), 5.62 (d, J = 3.5 Hz, 1H), 4.89 (d, J = 3.5 Hz, 1H), 1.70–1.20 (m, 12H), 1.19–0.95 (m, 3H), 0.83–0.34 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.3, 137.2, 129.3, 128.2, 127.7, 127.5, 127.4, 127.1, 91.6, 68.1, 60.3, 40.8, 35.3, 34.3, 20.4, 17.2.



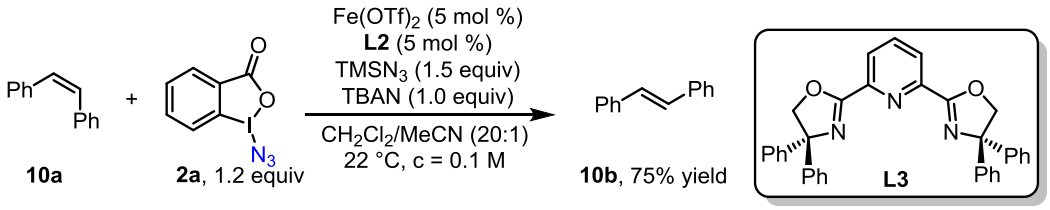
To a flame-dried 3-dram vial equipped with a stirring bar were added **2a** (69.4 mg, 0.24 mmol) and TEMPO (37.5 mg, 0.24 mmol). The vial was evacuated and backfilled with N_2 three times and anhydrous CH_2Cl_2 (1.5 mL) was added. After the vial was degassed with brief

evacuation and backfilled with N_2 twice, *cis*-stilbene **10a** (36 µL, 0.2 mmol) and $TMSN_3$ (40 µl, 0.3 mmol) were added successively to this vial at room temperature. The reaction was kept at room temperature for 2 h and then quenched with a saturated $NaHCO_3$ solution (0.1 mL), and further diluted with hexanes (3 mL). The mixture was stirred vigorously for 10 min and filtered through a short silica gel pad. The filtrate was concentrated *in vacuo* and the crude product was analyzed by ^1H NMR with trimethoxybenzene as an internal standard. **12** was also identified (69% yield, *dr*: 2.3:1).

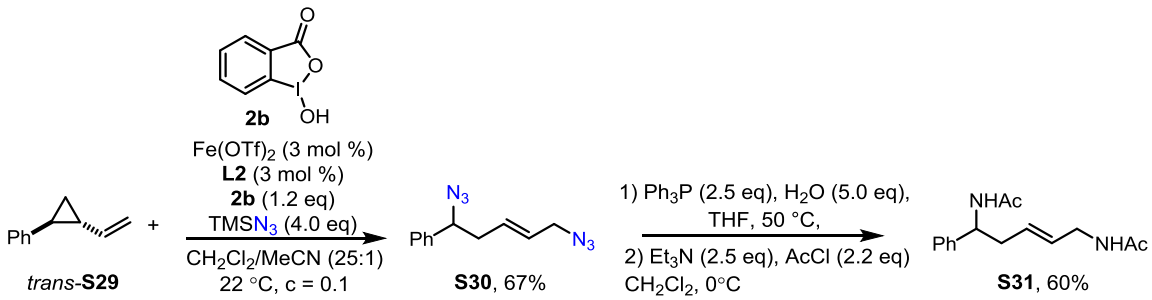


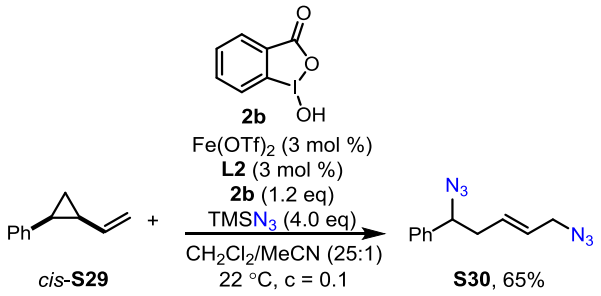
To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added $Fe(OTf_2)_2$ (3.5 mg, 0.01 mmol) and **L3** (5.2 mg, 0.01 mmol). After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (0.4 mL) and MeCN (0.1 mL) were added via a syringe and the mixture was stirred at room temperature for 10 min. To another flame-dried 3-dram vial (vial **B**) equipped with a stirring bar was added **2a** (69.4 mg, 0.24 mmol). This vial was evacuated and backfilled with N_2 three times and anhydrous CH_2Cl_2 (1.5 mL) was added. Both vials were degassed with brief evacuation and backfilled with N_2 twice and they were cooled to -15 °C. *cis*-Stilbene **10a** (36 µL, 0.2 mmol) and a stock solution of $TBAN_3$ (1.0 M in CH_2Cl_2, 300 µl, 0.3 mmol) were added to vial **B** successively and followed by drop-wise addition of the catalyst solution in vial **A**. The reaction was then kept at room temperature for 2 h and then quenched with saturated $NaHCO_3$ solution (0.1 mL), and further diluted with hexanes (3 mL). The mixture was stirred vigorously for 10 min and filtered through a short silica gel pad. The filtrate was concentrated *in vacuo* and the crude product was analyzed by ^1H NMR with

trimethoxybenzene as an internal standard. *cis*-Stilbene was almost fully recovered.



To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added $Fe(OTf_2)_2$ (3.5 mg, 0.01 mmol) and **L2** (2.7 mg, 0.01 mmol). After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (0.4 mL) and MeCN (0.1 mL) were added via a syringe and the mixture was stirred at room temperature for 10 min. To another flame-dried 3-dram vial (vial **B**) equipped with a stirring bar was added **2a** (69.4 mg, 0.24 mmol). This vial was evacuated and backfilled with N_2 three times and anhydrous CH_2Cl_2 (1.5 mL) was added. Both vials were degassed with brief evacuation and backfilled with N_2 twice and they were cooled to -15 °C. *cis*-Stilbene **10a** (36 µL, 0.2 mmol), a stock solution of $TBAN_3$ (1.0 M in CH_2Cl_2, 300 µl, 0.3 mmol) and $TMSN_3$ (40 µl, 0.3 mmol) were added to vial **B** successively and followed by drop-wise addition of the catalyst solution in vial **A**. The reaction was kept at room temperature for 2 h and then quenched with saturated $NaHCO_3$ solution (0.1 mL), and further diluted with hexanes (3 mL). The mixture was stirred vigorously for 10 min and filtered through a short silica gel pad. The filtrate was concentrated *in vacuo* and the crude product was analyzed by ^1H NMR with trimethoxybenzene as an internal standard. *trans*-stilbene was obtained in 75% yield.





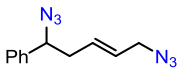
Scheme 69. Radical Clock of the Iron-Catalyzed Olefin Diazidation

Two isomeric vinyl-cyclopropane substrates were evaluated in order to determine whether a radical species is involved in the olefin diazidation. *trans*-2-Phenyl-1-vinylcyclopropane *trans*-**S29** was synthesized according to a literature procedure.[10, 83] *cis*-2-Phenyl-1-vinylcyclopropane *cis*-**29** was obtained according to another literature procedure.[10, 83b, 84]

To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added $Fe(OTf)_2$ (5.3 mg, 0.015 mmol) and **L2** (4.1 mg, 0.015 mmol). After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (0.8 mL) and MeCN (0.2 mL) were added via a syringe and the mixture was stirred at room temperature for 10 min. To another flame-dried 3-dram vial (vial **B**) equipped with a stir bar was added **2b** (158.4 mg, 0.60 mmol). This vial was evacuated and backfilled with N_2 three times and anhydrous CH_2Cl_2 (4.0 mL) was added. Both vials were degassed with brief evacuation and backfilled with N_2 twice. **S29** (72.1 mg, 0.5 mmol), $TMSN_3$ (263 μL, 2.0 mmol) were added successively to vial **B** and followed by drop-wise addition of the catalyst solution in vial **A** at room temperature. The reaction was kept at room temperature for 2 h and then quenched with a saturated $NaHCO_3$ solution (0.1 mL) and further diluted with hexanes (5 mL). The mixture was stirred vigorously for 10 min and filtered through a short silica gel pad. The filtrate was concentrated *in vacuo*. The residue was subsequently purified through a silica gel flash column (hexanes/Et_2O: from 200:1 to 50:1) and

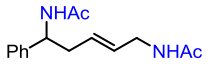
S30 was isolated as a colorless oil (76.4 mg, 67% yield).

S30 was obtained with essentially the same yield through the same procedure with *cis*-2-Phenyl-1-vinylcyclopropane *cis*-**S29**. Isomerization product *trans*-**S29** was not identified.



S30

(1,5-Diazidopent-3-en-1-yl)benzene (**S30**): IR ν_{max} (neat)/cm^{-1}: 2920 (w), 2096 (s), 1245 (m), 974 (w), 700 (w); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43–7.28 (m, 5H), 5.74–5.53 (m, 2H), 4.54–4.45 (m, 1H), 3.71 (d, J = 5.9 Hz, 2H), 2.69–2.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.0, 131.3, 129.0, 128.6, 127.0, 126.9, 65.9, 52.6, 39.2.



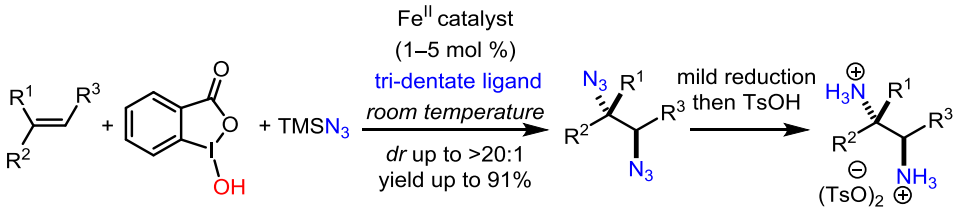
S31

***N*,*N*'-(5-Phenylpent-2-ene-1,5-diyl)diacetamide** (**S31**). To a 3-dram vial equipped with a stir bar were added diazidation product **S30** (45.6 mg, 0.2 mmol), THF (2 mL) and H_2O (18 μL, 1.0 mmol). After the vial was evacuated and backfilled with N_2 three times, a solution of PPh_3 (131.2 mg, 0.5 mmol) in THF (1 mL) was added drop-wise at 0 °C. The mixture was warmed up to 50 °C and stirred for 6 h (the reaction was monitored by IR until the absorption of azido groups disappeared). The mixture was then concentrated *in vacuo* and the residue was dissolved in CH_2Cl_2 (3 mL). This solution cooled to 0 °C and Et_3N (68 μL, 0.5 mmol) was then added via a syringe followed by drop-wise addition of acetyl chloride (32 μL, 0.44 mmol). The reaction was kept stirring for 1 h and quenched with saturated NH_4Cl solution (1 mL). After the organic layer was separated, the aqueous phase was extracted with CH_2Cl_2 (5 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford **S31** as colorless oil (31 mg, 60% yield). IR ν_{max} (neat)/cm^{-1}: 3288 (s), 1650 (s), 1549 (s), 1433

(w), 1374 (m), 1297 (m), 970 (w), 700 (w); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.18 (m, 5H), 6.08 (d, J = 7.0 Hz, 1H), 5.59–5.38 (m, 3H), 5.09 (dd, J = 14.6, 6.9 Hz, 1H), 3.73 (t, J = 4.0 Hz, 2H), 2.51 (t, J = 5.4 Hz, 2H), 2.00 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 169.6, 141.6, 129.6, 128.8, 128.5, 127.6, 126.7, 52.7, 41.5, 39.0, 23.5, 23.4; HRMS (ESI, m/z): calcd for $C_{15}H_{21}N_2O_2^+$, [M + H^+], 261.1598, found 261.1603.

4.3 RESULTS

Herein, we describe an iron-catalyzed diastereoselective olefin diazidation at room temperature with low catalyst loading (Scheme 70).[83b, 85] This new method tolerates a broad range of olefins, including those that are incompatible with existing methods. Notably, the anti-selectivity can be modulated by iron catalysts (d.r. up to >20:1). This method also provides a convenient approach to a variety of nitrogen-containing molecules, including vicinal primary diamines and 2-azido glycosyl azides, which are valuable for N-linked glycoprotein synthesis. Furthermore, preliminary mechanistic studies suggest that this reaction may proceed through a new selective pathway, which has the promise to become a general strategy for selective olefin difunctionalization.



Scheme 70. Iron-Catalyzed Olefin Diazidation

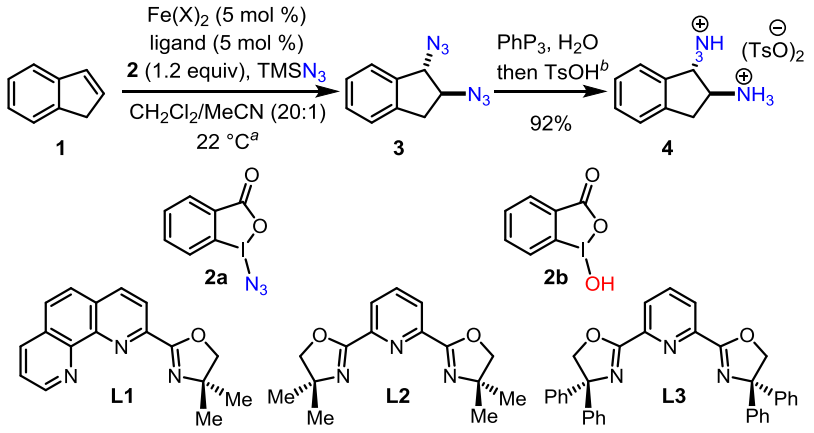
4.3.1 Iron Catalyst Discovery

Indene (**1**) was selected as a model substrate for catalyst discovery since it is incompatible with existing diastereoselective olefin diazidation methods. Azidoiodinane (**2a**) and $Fe(OTf)_2$ were initially selected as the azido-transfer reagent and the catalyst, respectively. We observed that $Fe(OTf)_2$ was ineffective for the azido-group transfer in the absence of $TMSN_3$ and both **1** and **2a** were fully recovered (Table **25**, entry 1). However, in the presence of $TMSN_3$, a catalytic amount of $Fe(OTf)_2$ was sufficient to turn over the catalytic cycle, thus affording the indene diazide **3** in high yields (entries 2, 4, and 5). Notably, in the absence of iron catalysts, no desired product was observed and **1** was fully recovered (entry 3). These observations suggest that $TMSN_3$ is necessary to activate **2a** for the azido-group transfer and that iron catalysts are also necessary for the olefin diazidation.

Although the $Fe(OTf)_2$/**L1** complex catalyzed a moderately diastereoselective reaction (entry 2), the d.r. value was significantly improved when the ligand **L2** was used (entry 4). Notably, a bulkier ligand (**L3**) induced a higher d.r. value (entry 5). Since **2a** is prepared from bench-stable benziodoxole (**2b**) with an excess amount of $TMSN_3$, and **2b** is barely soluble under the olefin diazidation conditions,[86] we explored using **2b** as the terminal oxidant under heterogeneous conditions (entry 6). To our pleasure, **3** was obtained with essentially the same yield and d.r. value under these new reaction conditions. This observation suggests that **2a** may be rapidly derived from **2b** *in situ*. Note that precautions with regard to handling $TMSN_3$ should be taken during the reaction workup.

We thereby evaluated the counterion effect and discovered that $Fe(NTf_2)_2$ was equally effective (Table **25**, entry 7). Surprisingly, the $Fe(OAc)_2$/**L3** complex catalyzed highly diastereoselective anti-diazidation of **1** with an excellent yield (entry 8). Since **3** is a convenient

precursor for the indene diamine, it is further converted into the anti-indene diaminium salt **4** in a high yield by a mild reduction/protonation sequence. Furthermore, standard resolution with tartaric acid readily provided the indene diamine essentially in its enantiopure form (97 % *ee*).



entry	$Fe(X)_2$	ligand	**2**	$TMSN_3$ (equiv)	time (h)	conversion[c]	yield (**3**)[d]	*dr* (**3**)[c]
1	$Fe(OTf)_2$	**L1**	**2a**	0	24.0	<5%	<5%	NA
2	$Fe(OTf)_2$	**L1**	**2a**	1.5	1.0	>95%	81%	3.7:1
3	none	**none**	**2a**	1.5	1.0	>95%	<5%	NA
4	$Fe(OTf)_2$	**L2**	**2a**	1.5	1.0	>95%	82%	7.1:1
5	$Fe(OTf)_2$	**L3**	**2a**	1.5	1.0	>95%	85%	8.5:1
6	$Fe(OTf)_2$	**L3**	**2b**	3.6	1.0	>95%	82%	8.6:1
7	$Fe(NTf_2)_2$	**L3**	**2b**	3.6	1.0	>95%	78%	8.0:1
8	$Fe(OAc)_2$	**L3**	**2b**	3.6	3.5	>95%	87%	>20:1

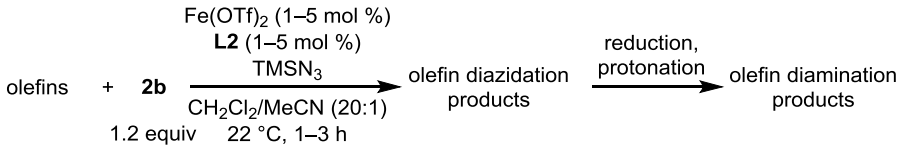
[a]Reactions were carried out under N_2 and then quenched with a saturated $NaHCO_3$ solution unless stated otherwise. [b]Reaction condition: PPh_3 (2.5 equiv), H_2O (5.0 equiv), THF, 50 °C, 2 h, then TsOH (2.5 equiv). [c]Conversion and dr were measured by **^{1}H NMR** analysis. [d]Isolated yield. OTf: trifluoromethanesulfonate, NTf2: trifluoromethanesulfonimide.

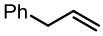
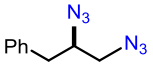
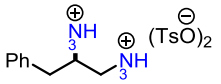
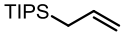
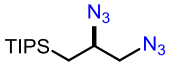
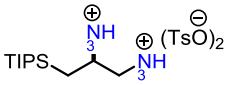
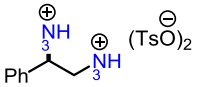
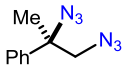
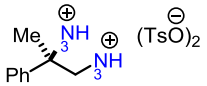
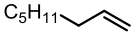
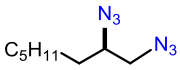
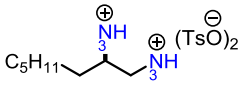
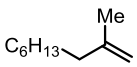
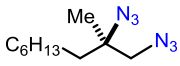
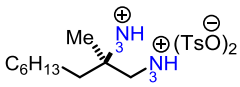
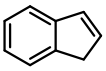
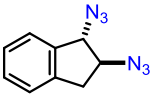
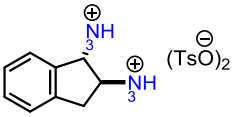
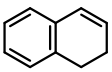
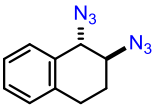
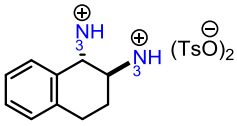
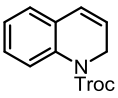
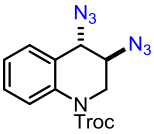
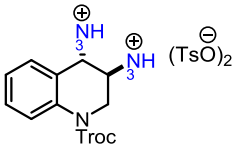
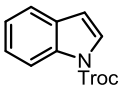
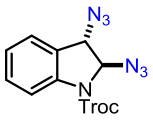
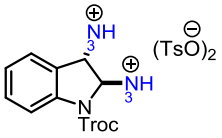
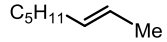
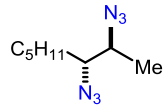
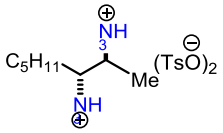
Table 25. Catalyst Discovery for the Diastereoselective Indene Diazidation

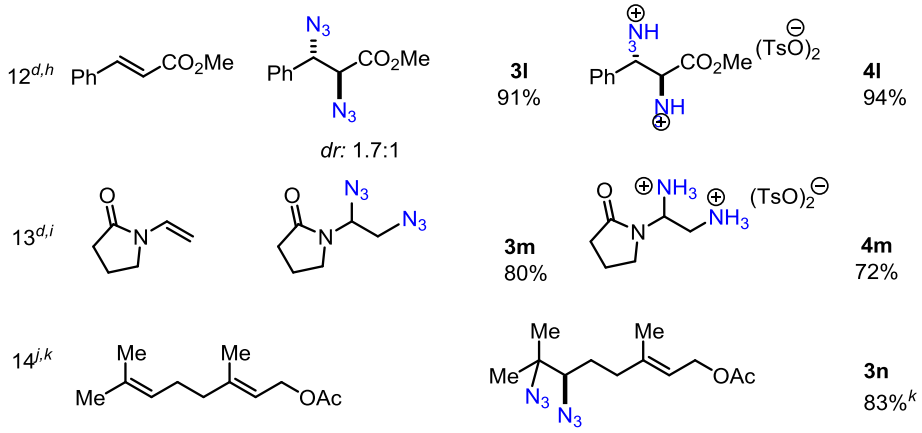
4.3.2 Substrate Scope

To examine the scope of this new iron-catalyzed olefin diazidation, we explored the reactivity with a broad range of olefins (Table **26**). Since the C/N ratios for these diazides generally vary from 1 to 3, careful isolation was executed strictly under small-scale (<100 mg) conditions. Additionally, direct diazide reduction without solvent concentration conveniently affords a variety of vicinal primary diamines. First, olefins with labile C-H bonds, including allyl

benzene and an allyl silane, were evaluated because they have been challenging substrates for the existing diazidation methods. For synthetic convenience, **L2**, with a lower molecular weight, was selected as the ligand for terminal olefins, and we discovered that the $Fe(OTf)_2$/**L2** complex catalyzed the efficient diazidation: the amount of competing direct C-H azidation product is less than 5% (entries 1 and 2). Mild derivatization converted the diazides into functionalized diaminium salts with excellent yields. Styrenyl and aliphatic terminal olefins are also excellent substrates: the corresponding diazides were isolated with good yields (entries 3–6). Next, we evaluated a range of cyclic olefins and discovered that the $Fe(OAc)_2$/**L3** complex is effective for highly diastereoselective diazidation of indene, dihydronaphthalene, dihydroquinoline, and indole (entries 7–10). Standard derivatization afforded a range of valuable anti-vicinal diamines, which are challenging to synthesize with existing diazidation or diamination methods. Further evaluation of acyclic internal olefins revealed that *trans*-2-octene is an excellent substrate for the diazidation yet with a low *dr* value (entry 11). Fortunately, the diastereomers were separable and the straightforward derivatization converted them into vicinal primary diamines, which are difficult to obtain with the existing olefin diamination methods. We also observed that an electron-deficient cinnamate ester is an excellent substrate, and an electron-rich enamide is also compatible with this method (entries 12 and 13). We further evaluated geranyl acetate and observed that the diazidation occurred regioselectively at the distal position with a more electron-rich olefin (entry 14).



entry[a]	olefin	diazide	yield[b] (1st step)	diammonium salt	yield[b] (2nd step)
1[c,d]			**3b** 72%		**4b** 93%
2[d]			**3c** 89%		**4c** 90%
3[d]			**3d** 85%		**4d** 94%
4[e]			**3e** 83%		**4e** 90%
5[d]			**3f** 78%		**4f** 85%
6[e]			**3g** 88%		**4g** 94%
7[d,f]		 *dr* >20:1	**3a** 82%		**4a** 92%
8[d,f]		 *dr*: 12:1	**3h** 79%		**4h** 90%
9[e,g]		 *dr* >20:1	**3i** 66%		**4i** 89%
10[e,h]		 *dr* >20:1	**3j** 81%		**4j** 90%
11[d,h]		 *dr*: 1.4:1	**3k** 78%		**4k** 95%

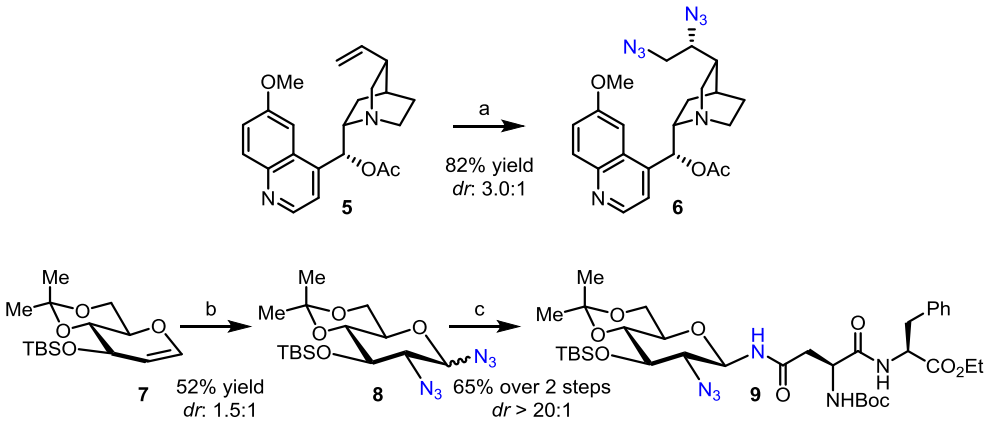


[a]$TMSN_3$ (3.6 4.0 equiv) was used. [b]Isolated yield. [c]$Fe(OTf)_2$·**L2** (1 mol %), 2 h. [d]PPh_3, H_2O, 50 °C, then TsOH. [e]Pd/C, H_2 22 °C, then TsOH. [f]$Fe(OAc)_2$·**L3** (5 mol %), 4 h. [g]$Fe(NTf_2)_2$·**L3** (10 mol %), 4 h. [h]$Fe(OTf)_2$·**L3** (5 mol %). [i]PMe_3, H_2O, 50 °C, then TsOH. [j]0 °C, 10 h. [k]92% yield for reduction.

Table 26. Substrate Scope for the Iron-Catalyzed Olefin Diazidation

4.3.3 Late Stage Functionalization

Furthermore, we explored this new method with densely functionalized olefins (Scheme **71**). Acetyl quinine (**5**) smoothly participates in the diazidation to afford diazide 6, which adds a new structural motif for organocatalysis. Additionally, glycal **7** is also a reasonable substrate, which affords 2-azido glycosyl azides **8**. Interestingly, both diastereomers were elaborated to 2-azido N-linked glycopeptide **9** as a single diastereomer via a reduction/ligation procedure. Notably, **9** is also a valuable building block for N-linked glycoprotein synthesis.[87]

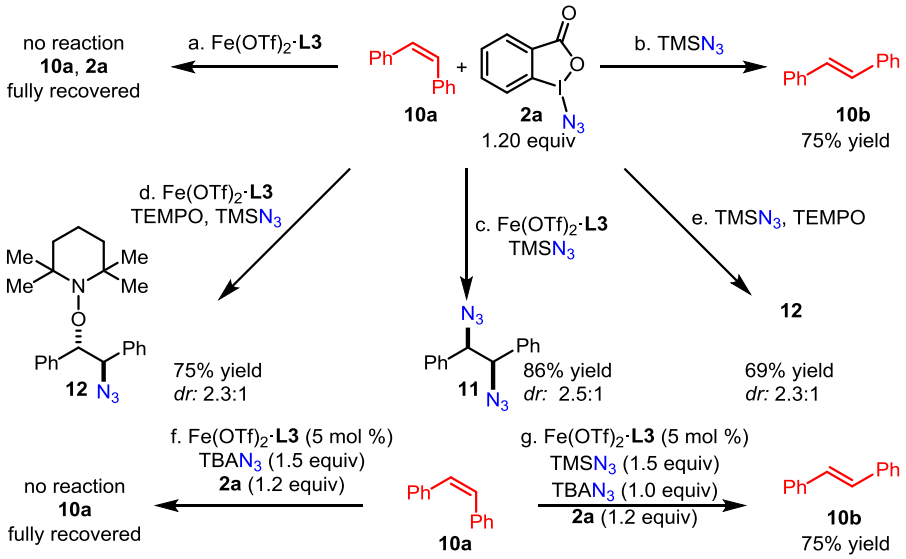


[a]$Fe(OTf)_2$·**L2** (10 mol %), 2b, $TMSN_3$, 22 °C; 82% yield, dr: 3:1. [b]$Fe(OTf)_2$·**L2** (5 mol %), 2b, $TMSN_3$, 0 °C; 52% yield, dr: 1.5:1. [c]PMe_3 in THF, -60-22 °C; then H_2O in THF, 40 °C; 76% yield, dr>20:1; then HATU, DIPEA, the corresponding peptide acid, DMF, 22 °C, 86% yield for the ligation step.

Scheme 71. Iron-Catalyzed Diazidation of Acetyl Quinine and Glycals for *N*-Linked Glycopeptide Synthesis

4.3.4 Mechanistic Working Hypothesis

The observed catalyst-controlled diastereoselectivity is mechanistically important because it suggests that iron catalysts are involved in the *dr*-determining step. Therefore, we selected cis-stilbene **10a** as a probe for several control experiments (Scheme **72**). First, when $TMSN_3$ is absent, no reaction was observed and both **10a** and **2a** were fully recovered (equation **72a**). Next, under an iron-free condition yet in the presence of $TMSN_3$, **10a** was isomerized to *trans*-stilbene **10b** and no diazidation product was observed (equation **72b**). We further discovered that **10a** was converted to diazide **11** under a standard condition and essentially the same *dr* was observed compared with the one obtained from **10b** (equation **72c**). Furthermore, **12** was obtained in the presence of TEMPO (equations **72d** and **72e**). These experiments provided several mechanistic insights. First, $TMSN_3$ is crucial to activate **2a**. Next, an azido-radical species is possibly involved in the olefin diazidation and a reversible radical addition may convert **10a** to a carbo-radical species under both standard and iron-free conditions. Additionally, this radical can be captured by TEMPO. Moreover, stereo-convergent diazidation of *cis/trans* stilbenes suggest that the second azido-group transfer may be rate-limiting.



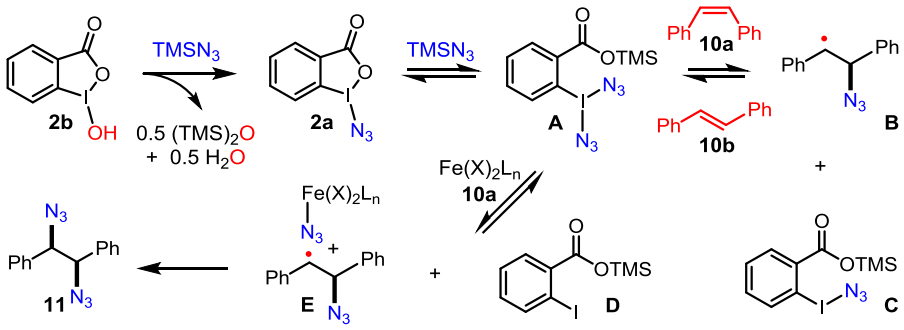
[a]Fe(OTf)$_2$·**L3** (5 mol %). [b]TMSN$_3$. [c]Fe(OTf)$_2$·**L3** (5 mol %), TMSN$_3$. [d]Fe(OTf)$_2$·**L3** (5 mol %), TMSN$_3$, TEMPO. [e]TMSN$_3$, TEMPO. [f]Fe(OTf)$_2$·**L3** (5 mol %), TBAN$_3$, **2a**, -15-22 °C. [g]Fe(OTf)$_2$·**L3** (5 mol %), TBAN$_3$, TMSN$_3$, **2a**, -15-22 °C. Other reactions were carried out at 22 °C.

Scheme 72. Control Experiments for Mechanistic Insights of the Iron-Catalyzed Olefin Diazidation

In order to probe for the role of TMSN$_3$, it was further replaced by TBAN$_3$ (equation **72f**). Surprisingly, no diazidation was observed and **10a** was fully recovered. However, in the presence of both TMSN$_3$ and TBAN$_3$, **10a** was isomerized to **10b** and no diazidation was observed (equation **72g**). These observations suggest that the Lewis-acidic TMS group is crucial for the activation of **2a** and that an excess amount of azide anion may deactivate iron catalysts.

Based on the collective evidence from the aforementioned control experiments and key observations in catalyst discovery (Table **10**), we propose a mechanistic working hypothesis that is supported by the experimental data (Scheme **73**). First, TMSN$_3$ reacts with **2b** and possibly converts **2b** to **2a** in situ. Next, **2a** may be further activated by TMSN$_3$ to reversibly generate intermediate **A**. In the absence of iron catalysts, **A** may react with *cis*-stilbene **10a**, presumably through reversible azido-radical addition, affording a carbo-radical species **B** and azidoiodobenzene **C**. Nevertheless, **B** may not be further oxidized in the absence of iron and the elimination from **B** will afford more stable **10b** and regenerate **A**. However, in the presence of an

iron catalyst, it may reductively cleave the I–N_3 bond of A, which presumably generates a high-valent iron species and an azido-radical. The azido-radical may thereby react with **10a** to afford another carbo-radical species **E** that is associated with the iron catalyst. Since the *dr* of olefin diazidation can be modulated both by the ligand and counter ion of the catalyst, it is likely that the high-valent iron species may further oxidize **E** through inner-sphere azido ligand-transfer to afford the diazide **11**.[46]



Scheme 73. Mechanistic Working Hypothesis for the Iron-Catalyzed Olefin Diazidation Using Benziodoxole and $TMSN_3$

4.4 CONCLUSIONS

In conclusion, we have discovered a new iron-catalyzed diastereoselective olefin diazidation method which tolerates a broad range of olefins, including those that are incompatible with the existing methods. It can also afford a variety of synthetically valuable building blocks that are difficult to prepare with alternative methods. Our mechanistic studies suggest that the reaction may proceed through a new pathway in which Lewis-acid activation is indispensable for the first azido-group transfer and that iron catalysts are crucially involved with the second azido-group transfer. Our current efforts focus on the mechanistic understanding of this new reaction and achieving effective asymmetric induction through new catalyst discovery.

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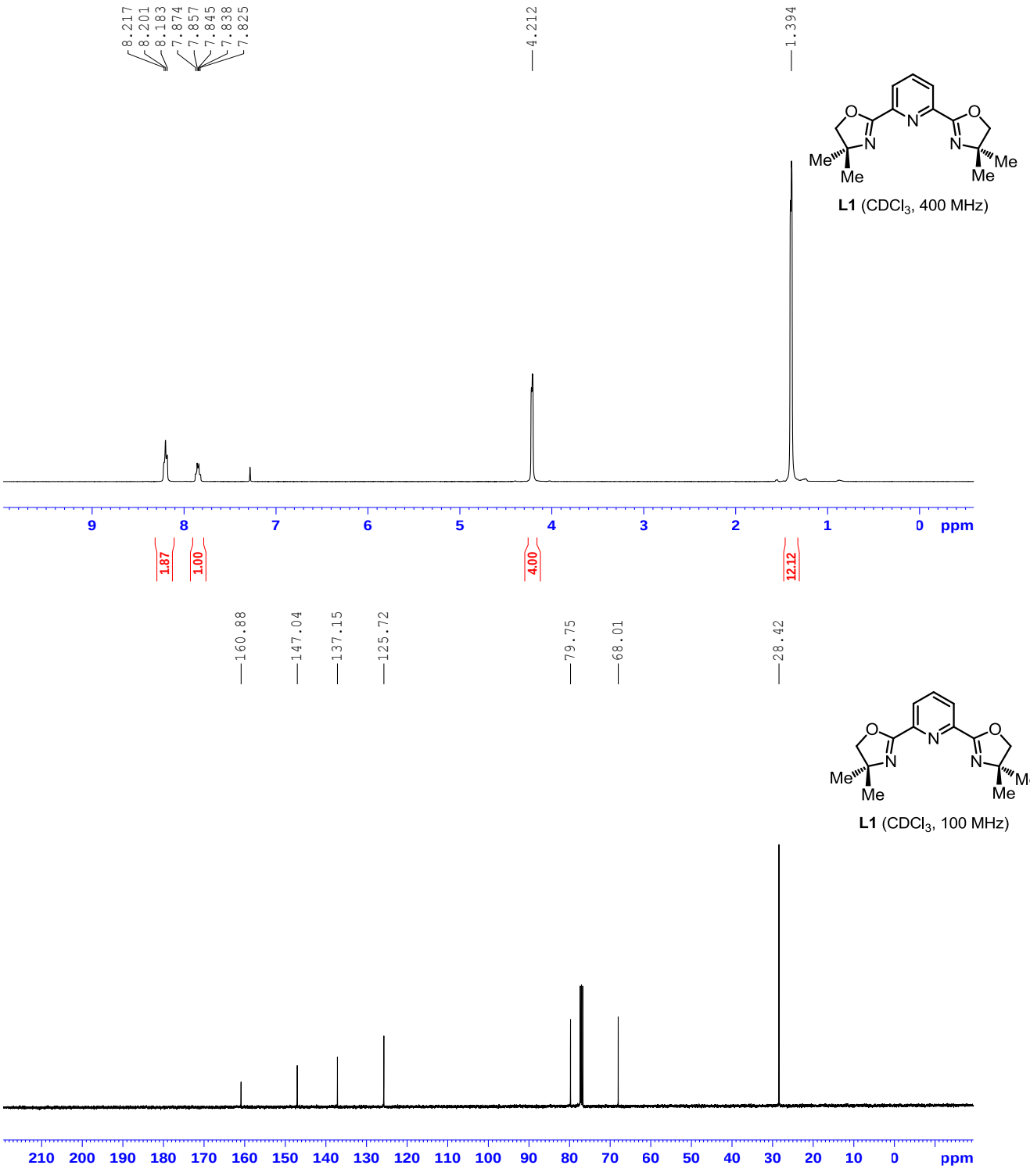
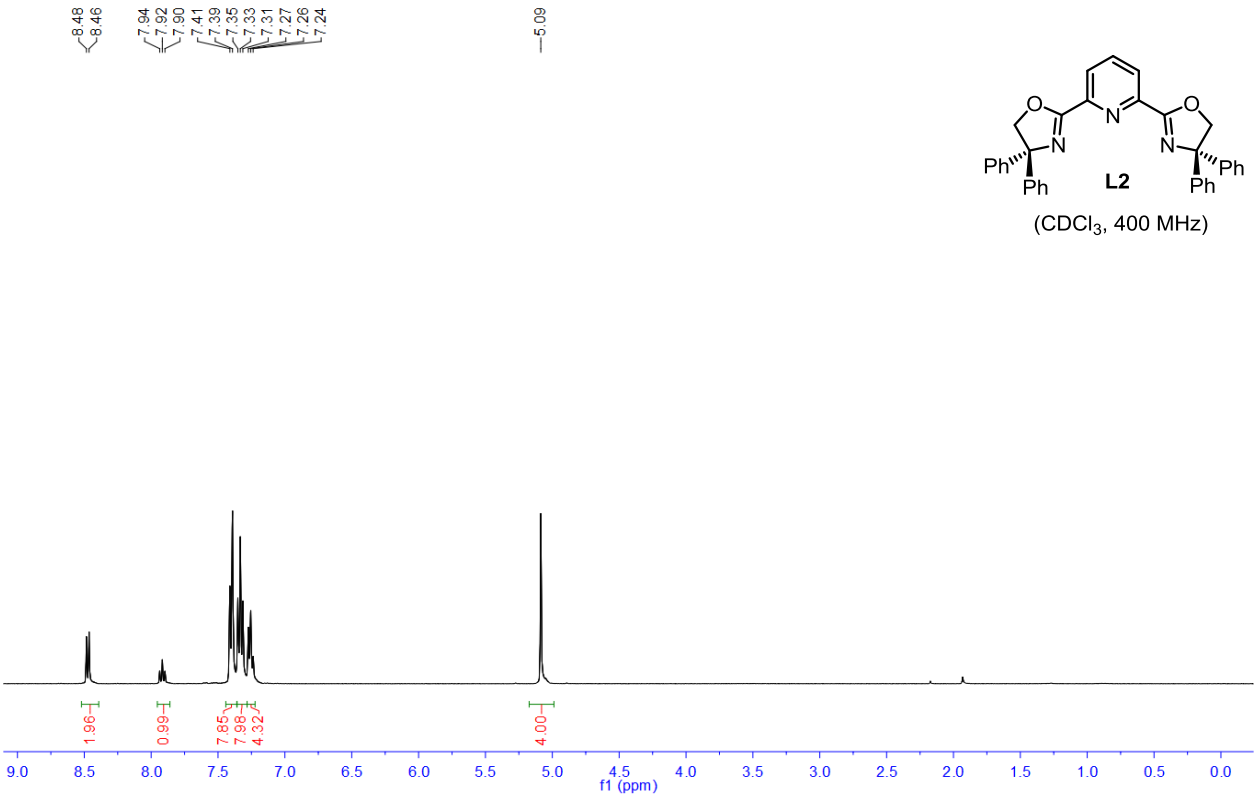
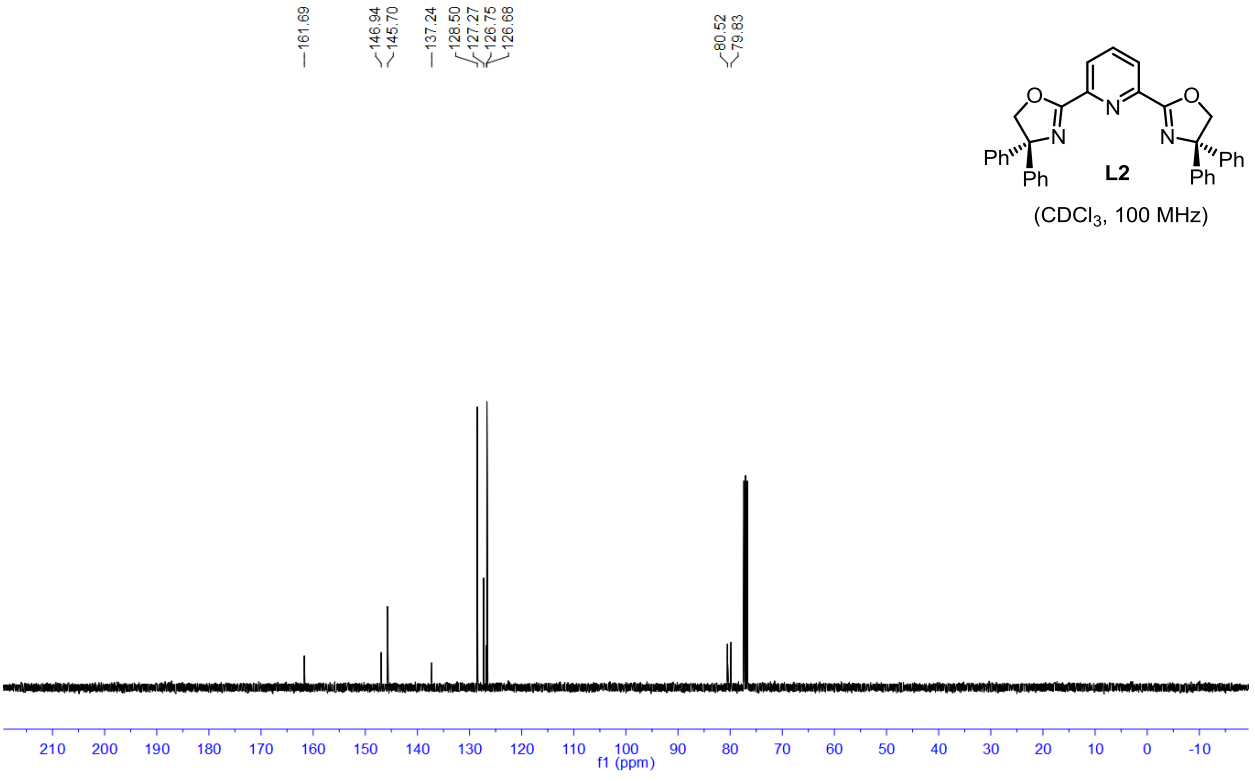
APPENDICES

Appendix A ^{1}H and ^{13}C Spectra of Compounds in Chapter I

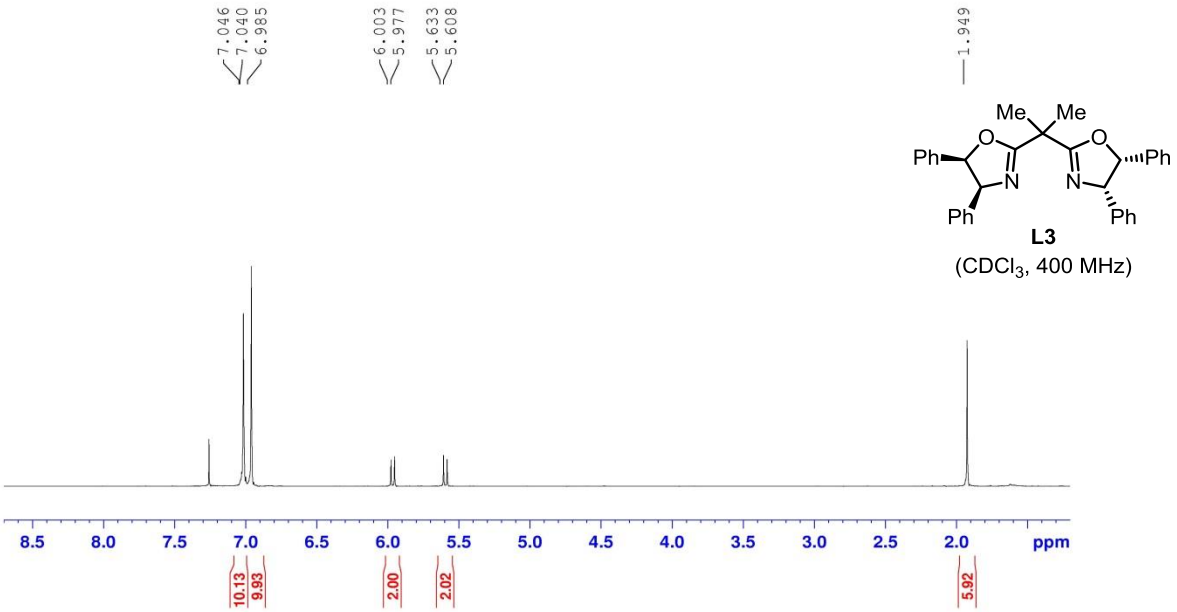




($CDCl_3$, 400 MHz)

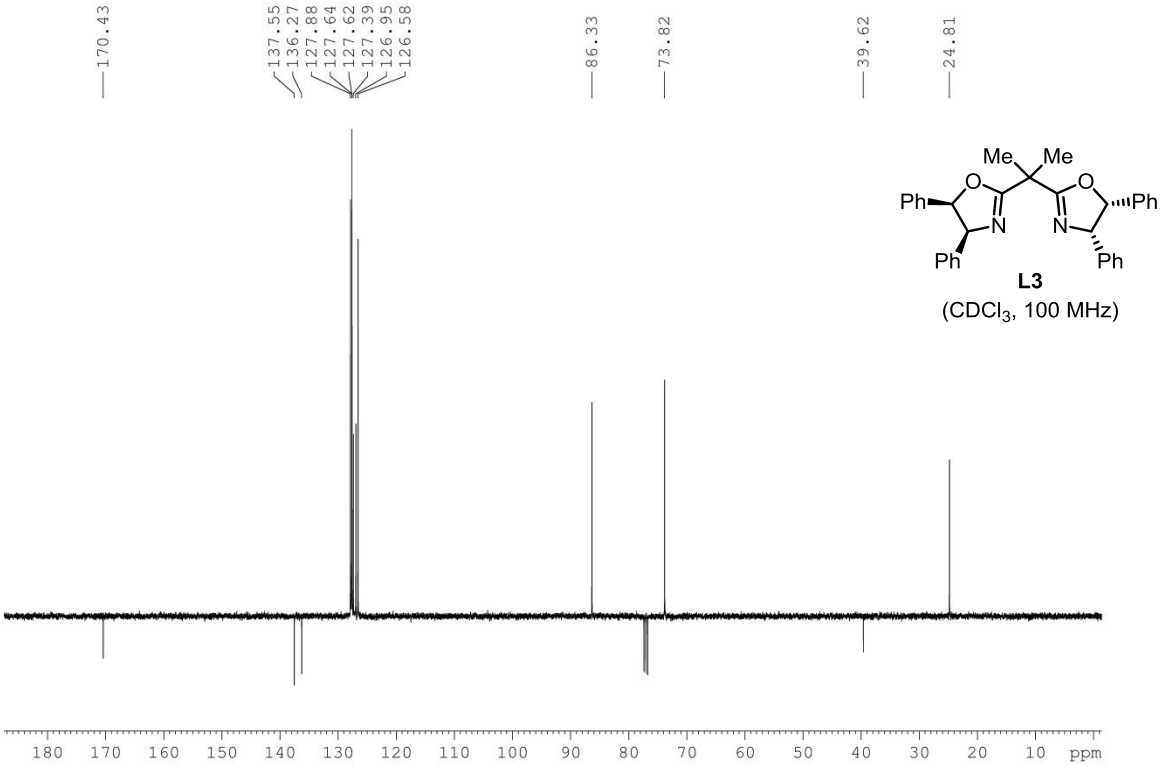


($CDCl_3$, 100 MHz)



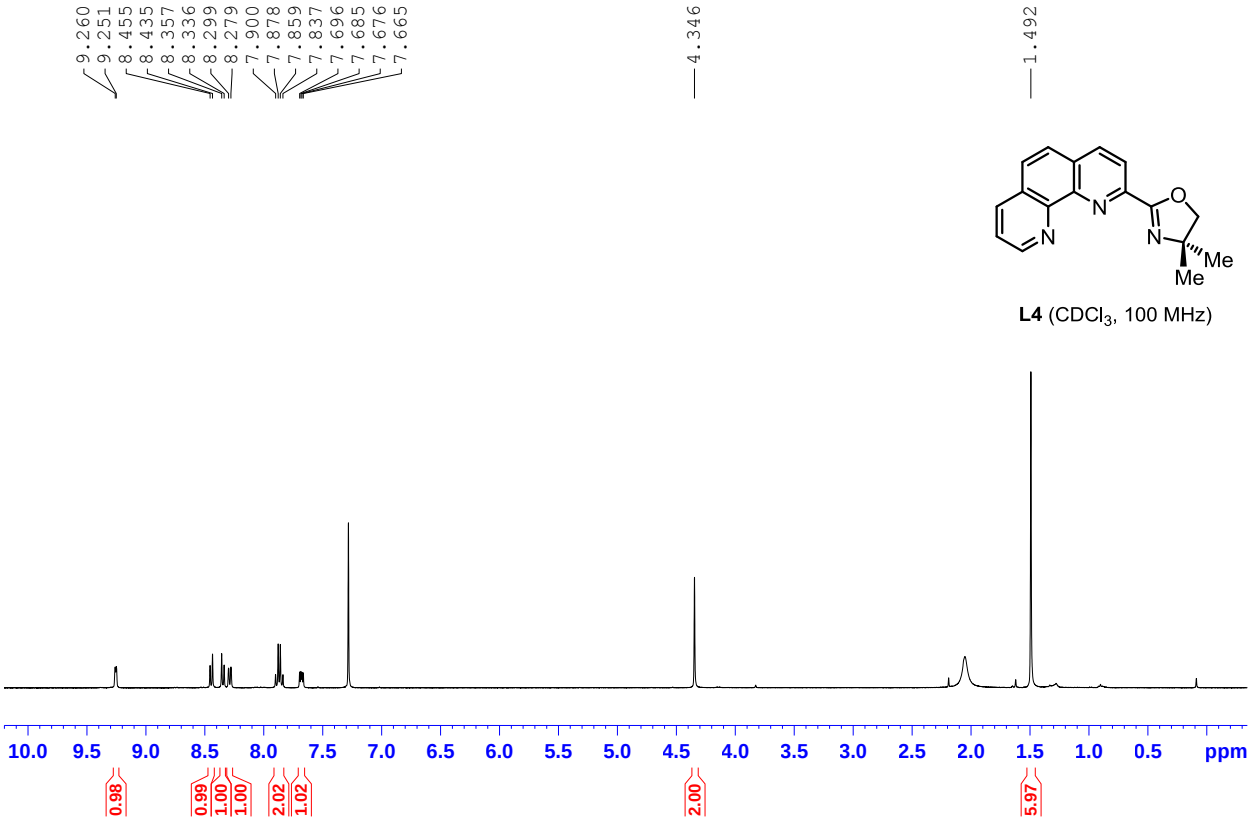
L3

($CDCl_3$, 400 MHz)

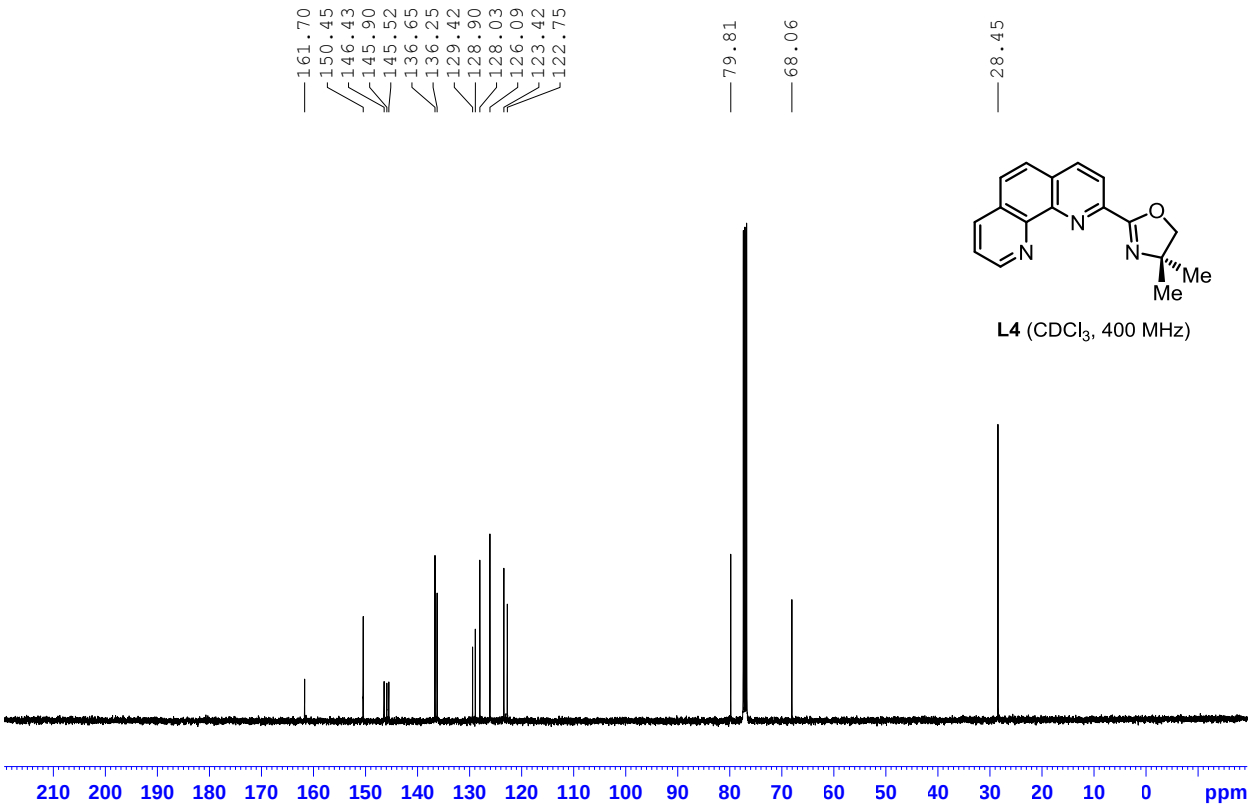


L3

($CDCl_3$, 100 MHz)

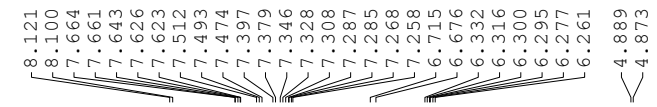


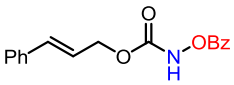
L4 ($CDCl_3$, 100 MHz)



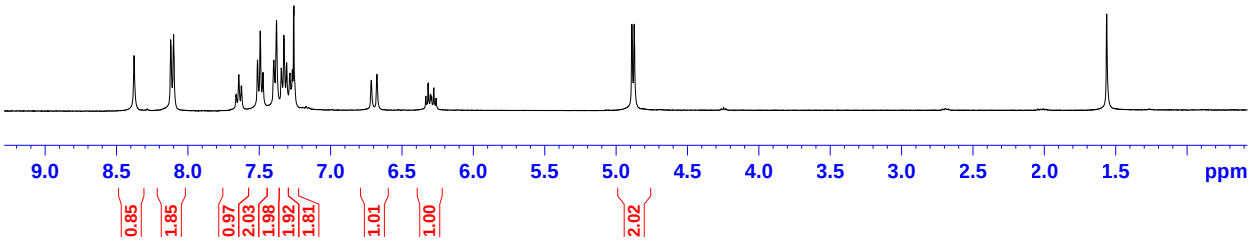
L4 ($CDCl_3$, 400 MHz)

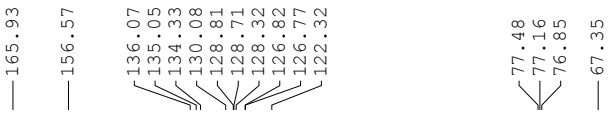
Appendix B ^{1}H and ^{13}C Spectra of Compounds in Chapter II

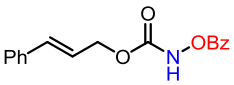




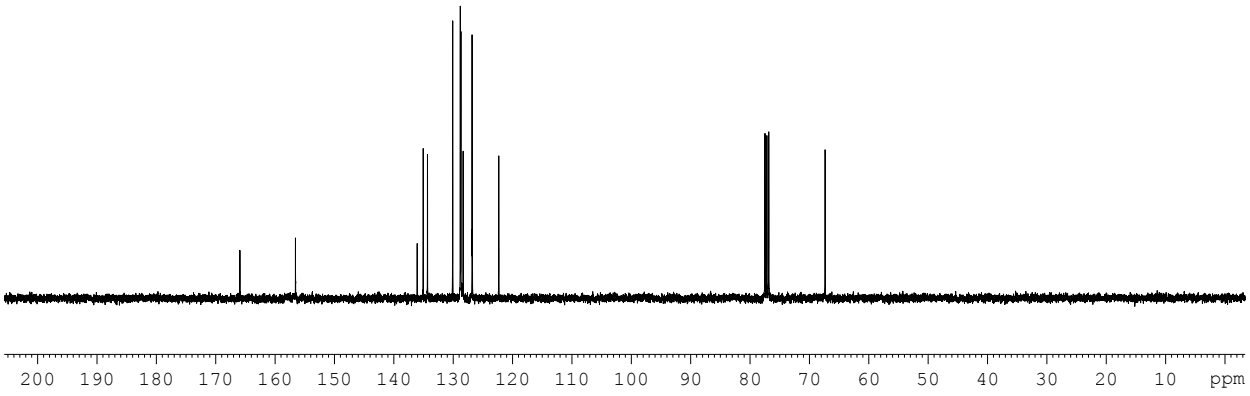
S3-1 ($CDCl_3$, 400 MHz)

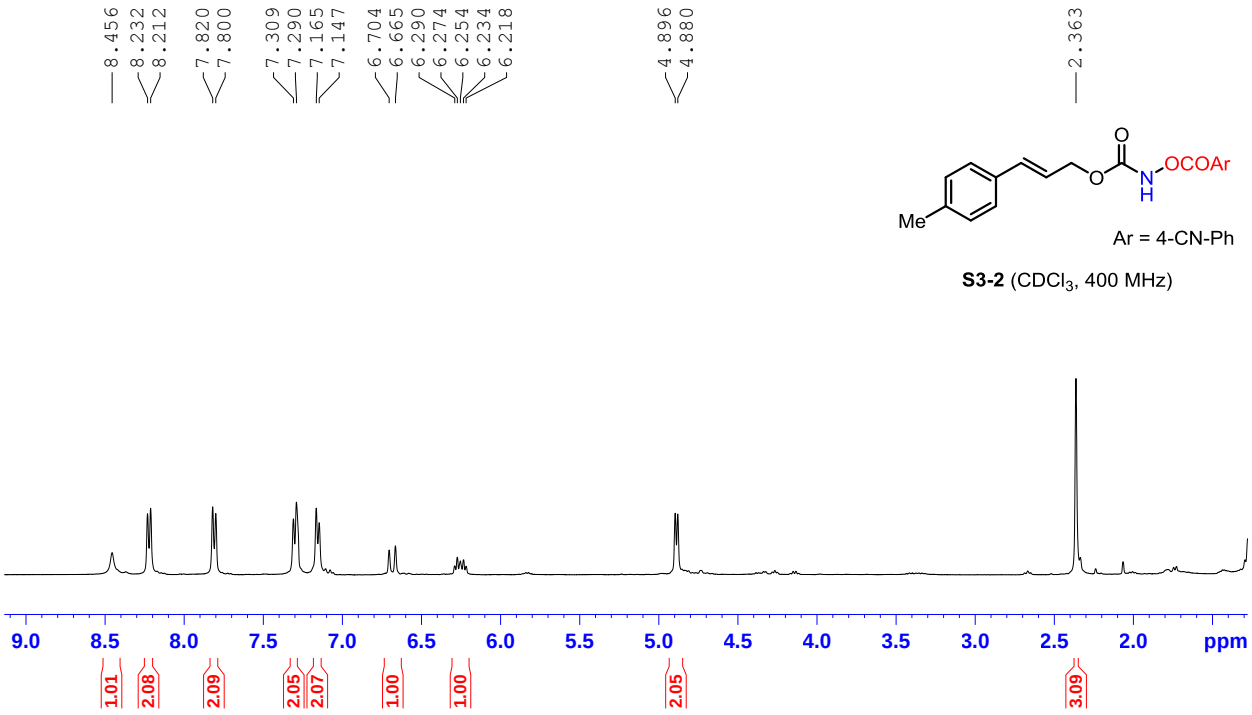




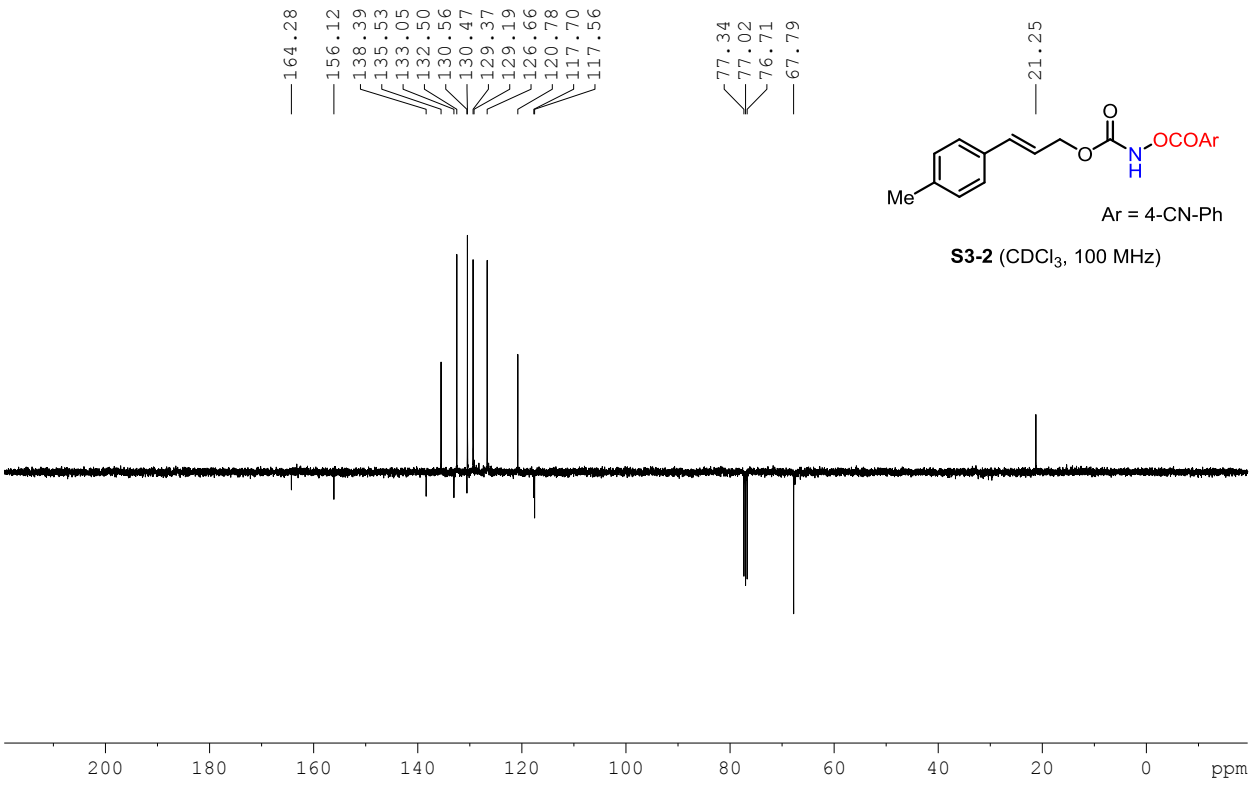


S3-1 ($CDCl_3$, 100 MHz)

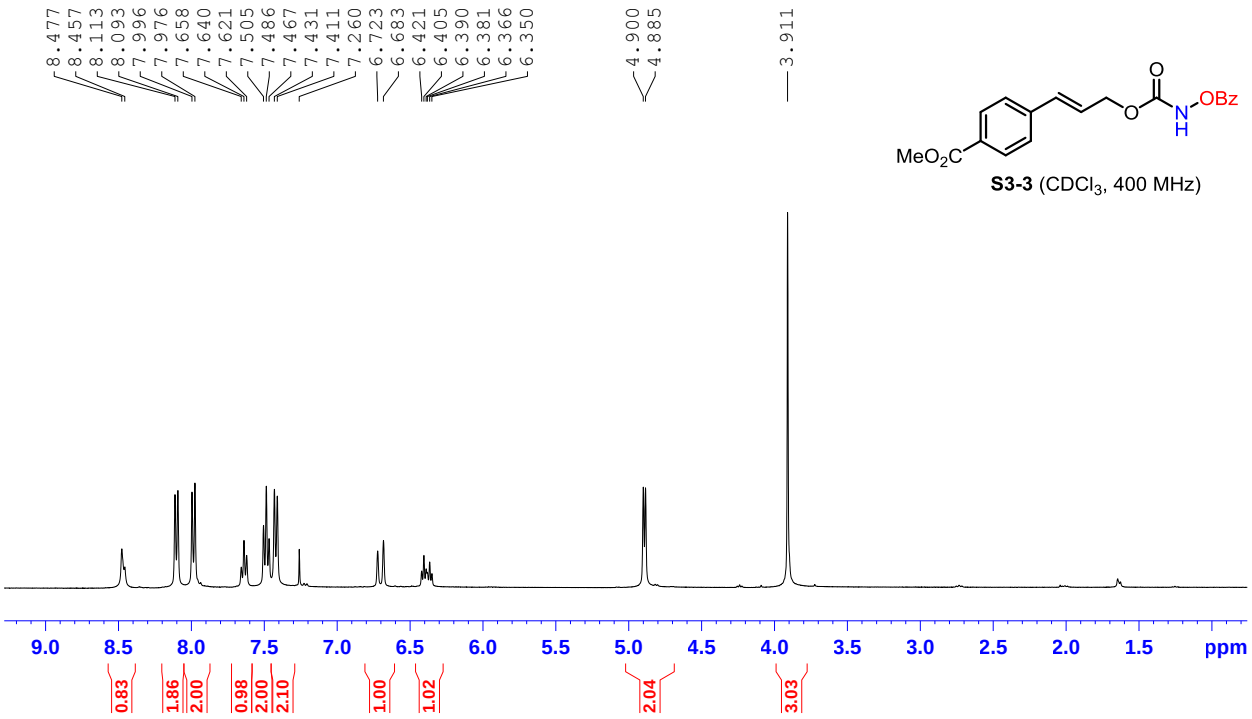




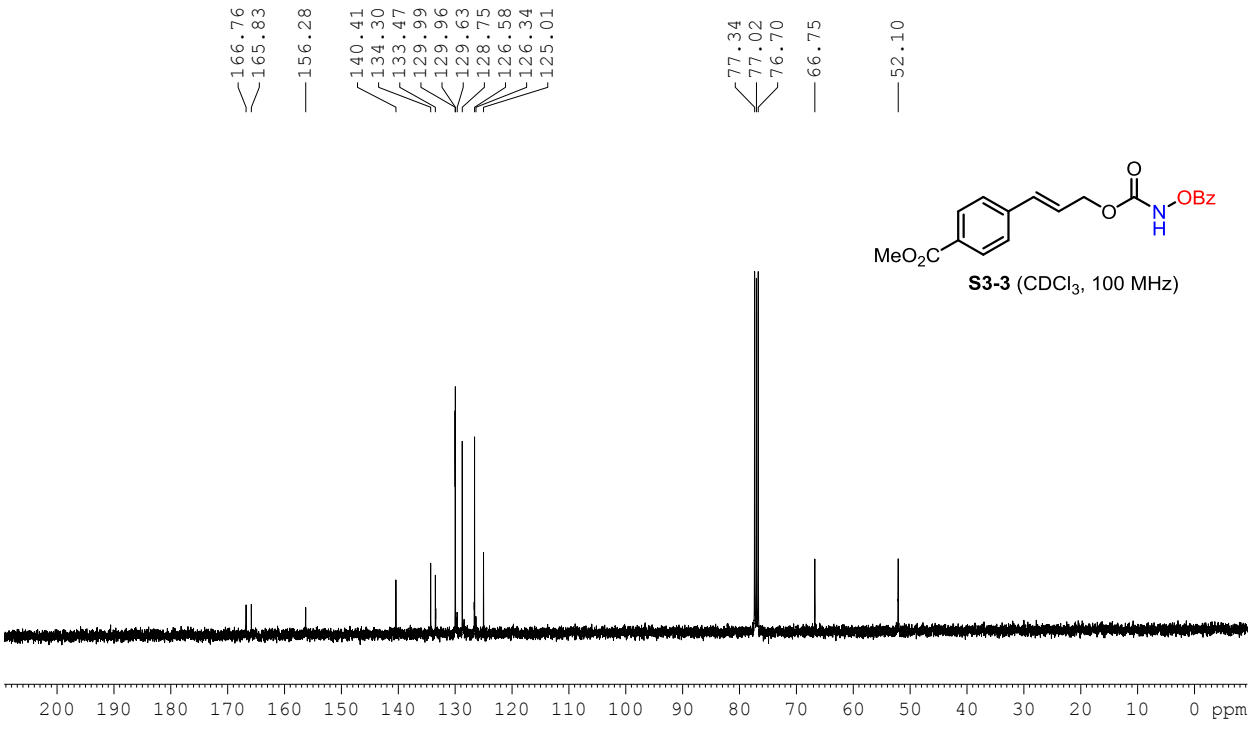
S3-2 ($CDCl_3$, 400 MHz)



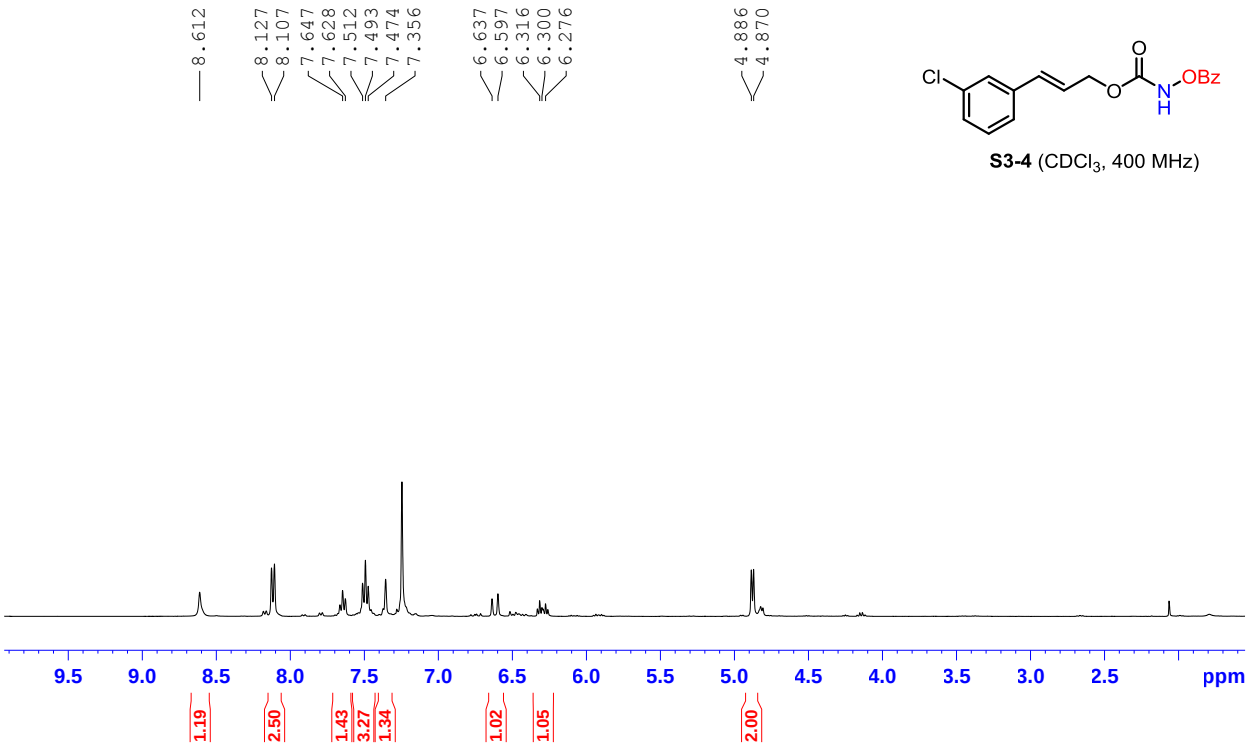
S3-2 ($CDCl_3$, 100 MHz)



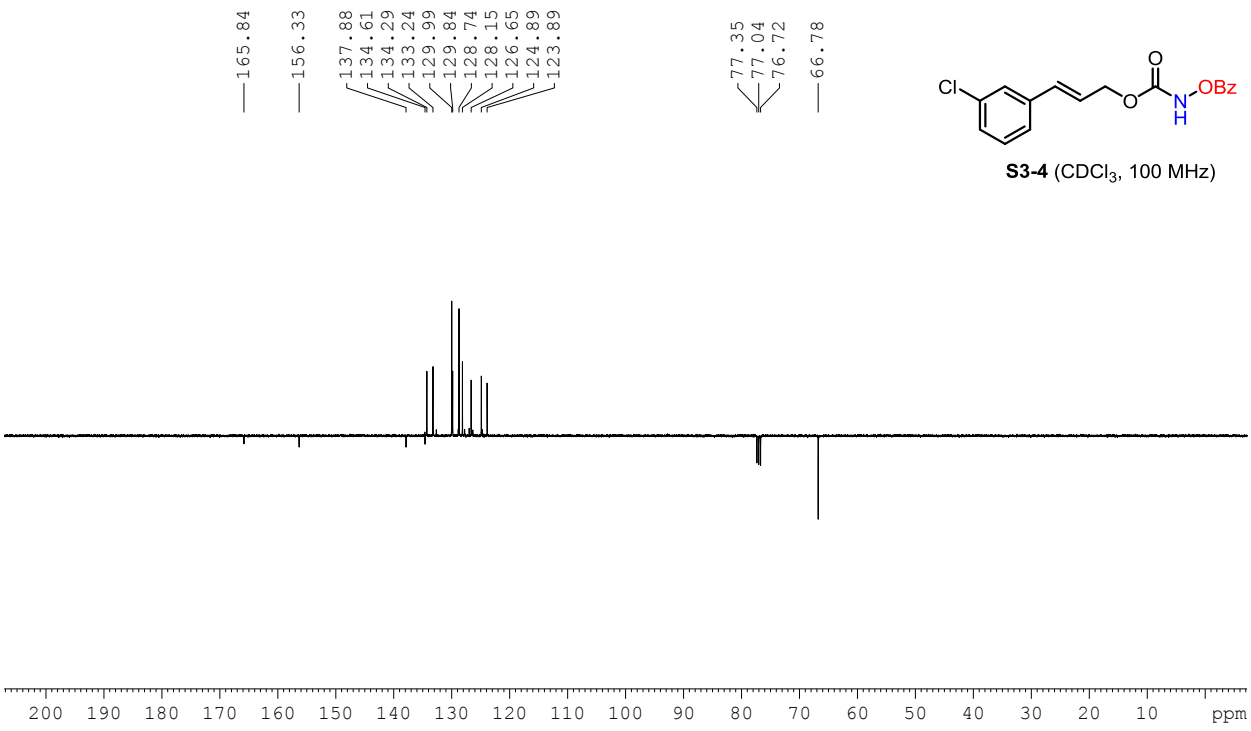
S3-3 ($CDCl_3$, 400 MHz)



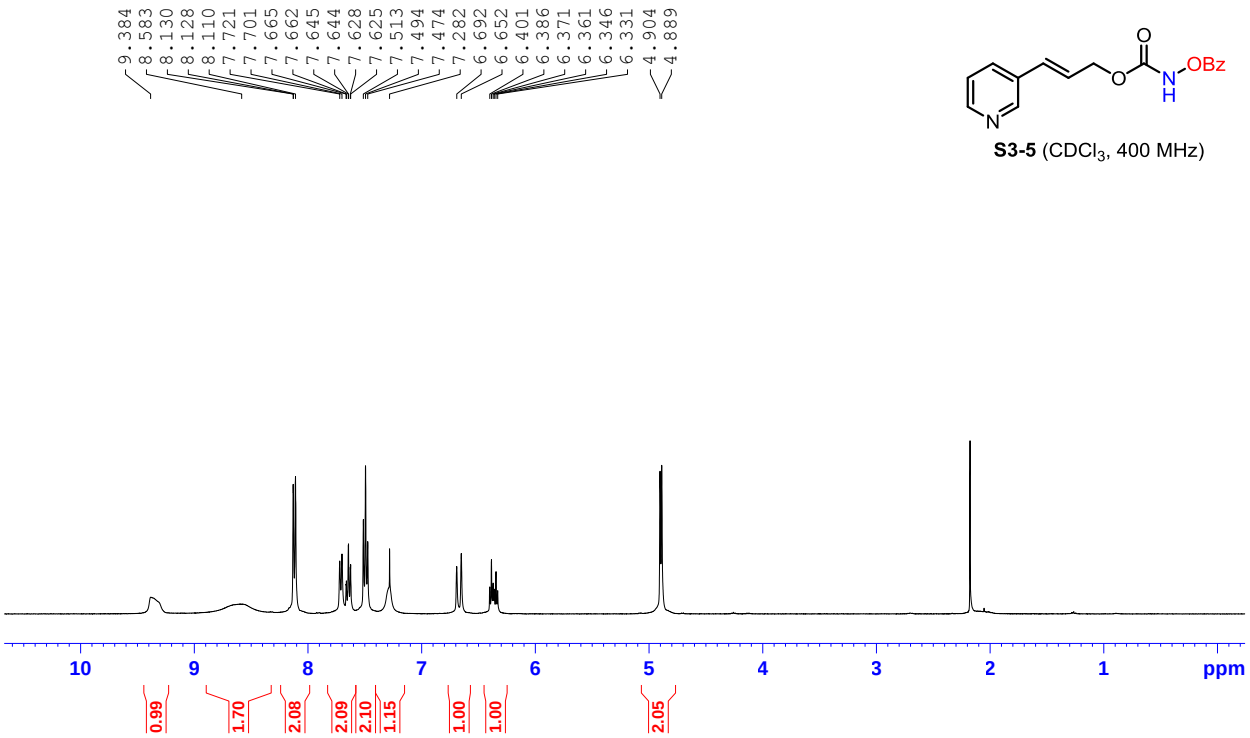
S3-3 ($CDCl_3$, 100 MHz)



S3-4 ($CDCl_3$, 400 MHz)



S3-4 ($CDCl_3$, 100 MHz)



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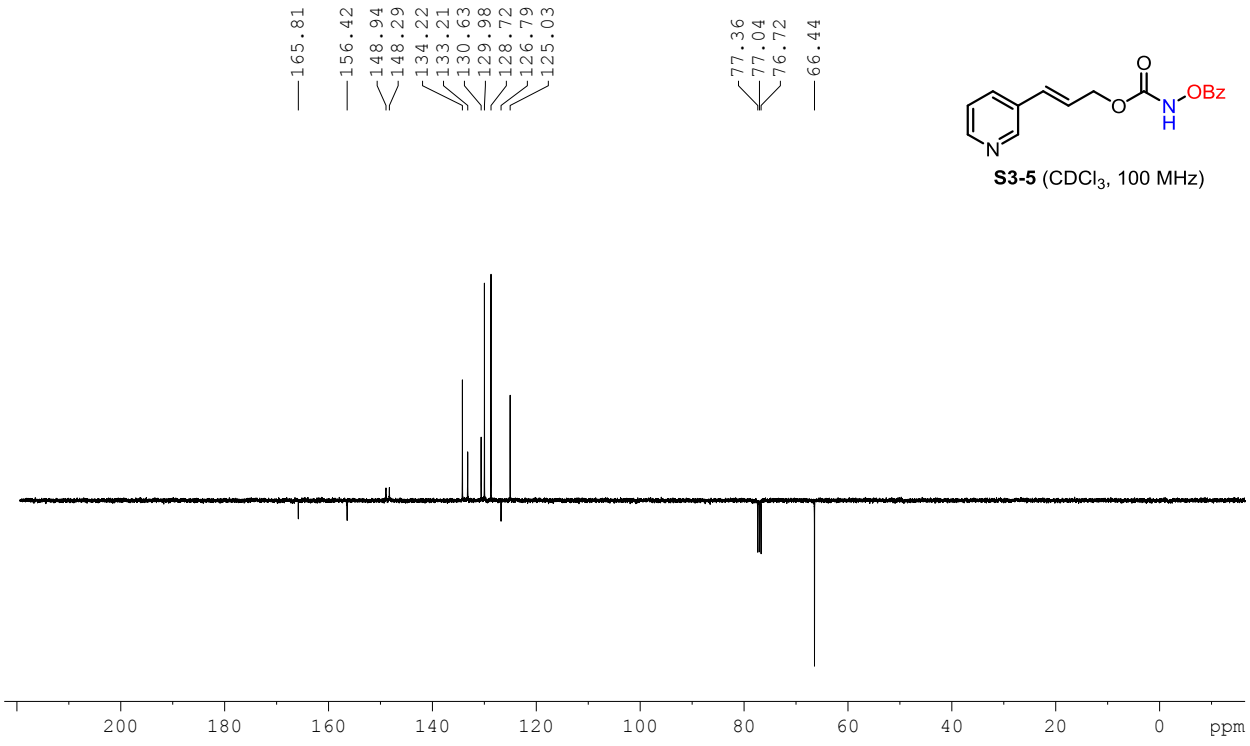

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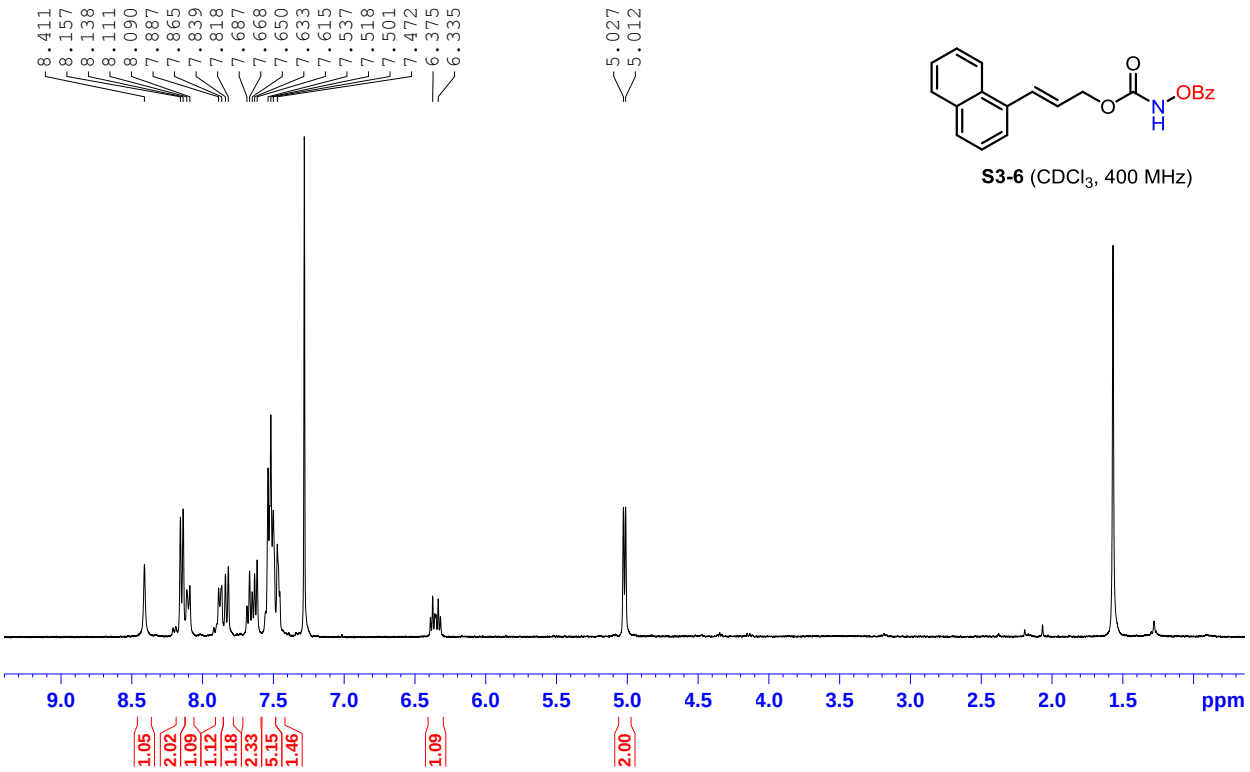

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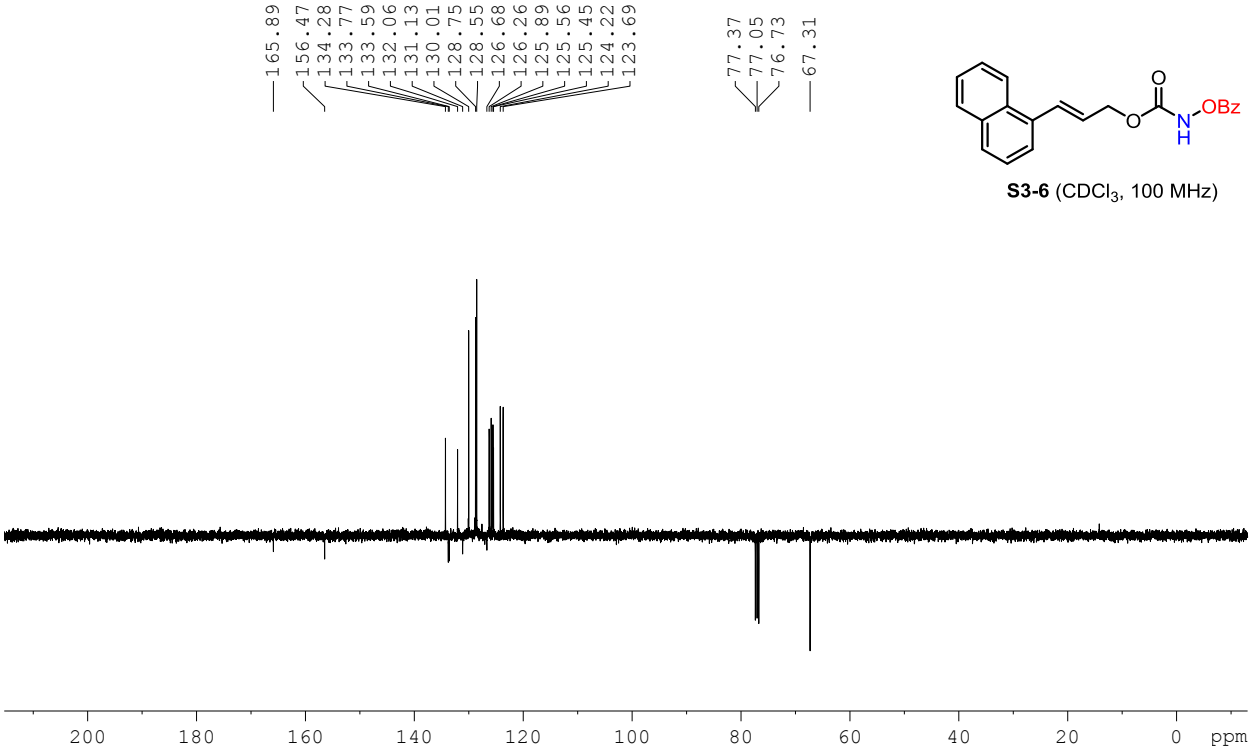

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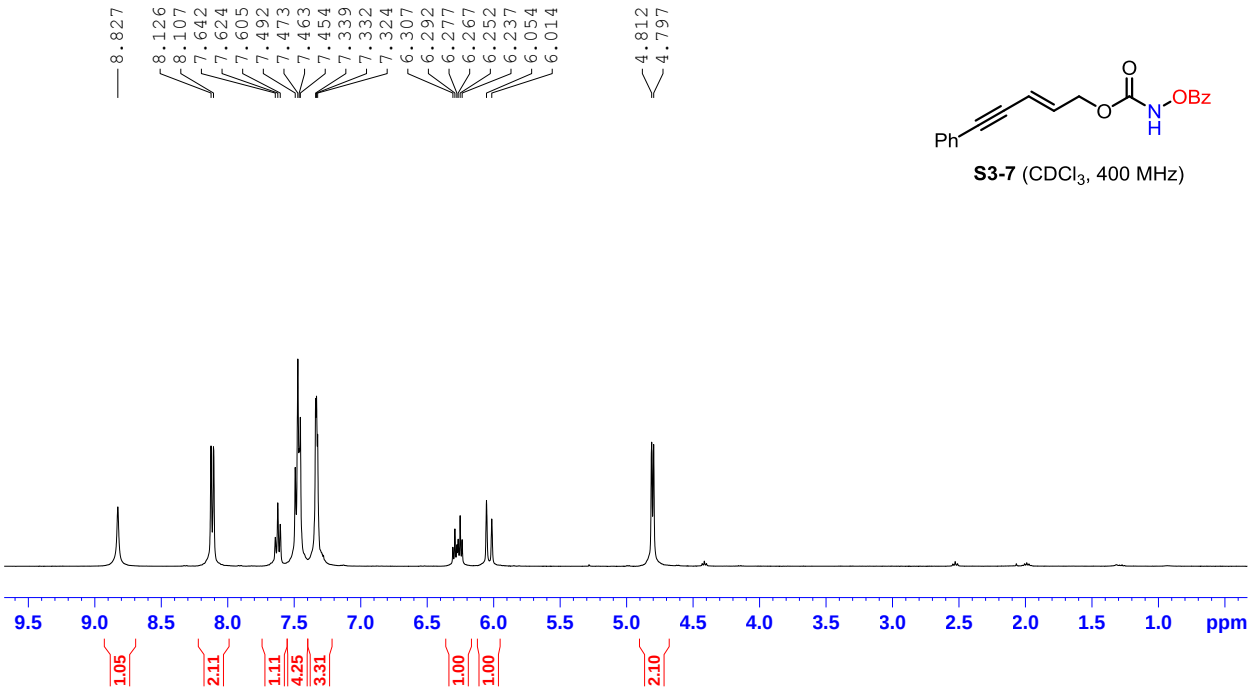

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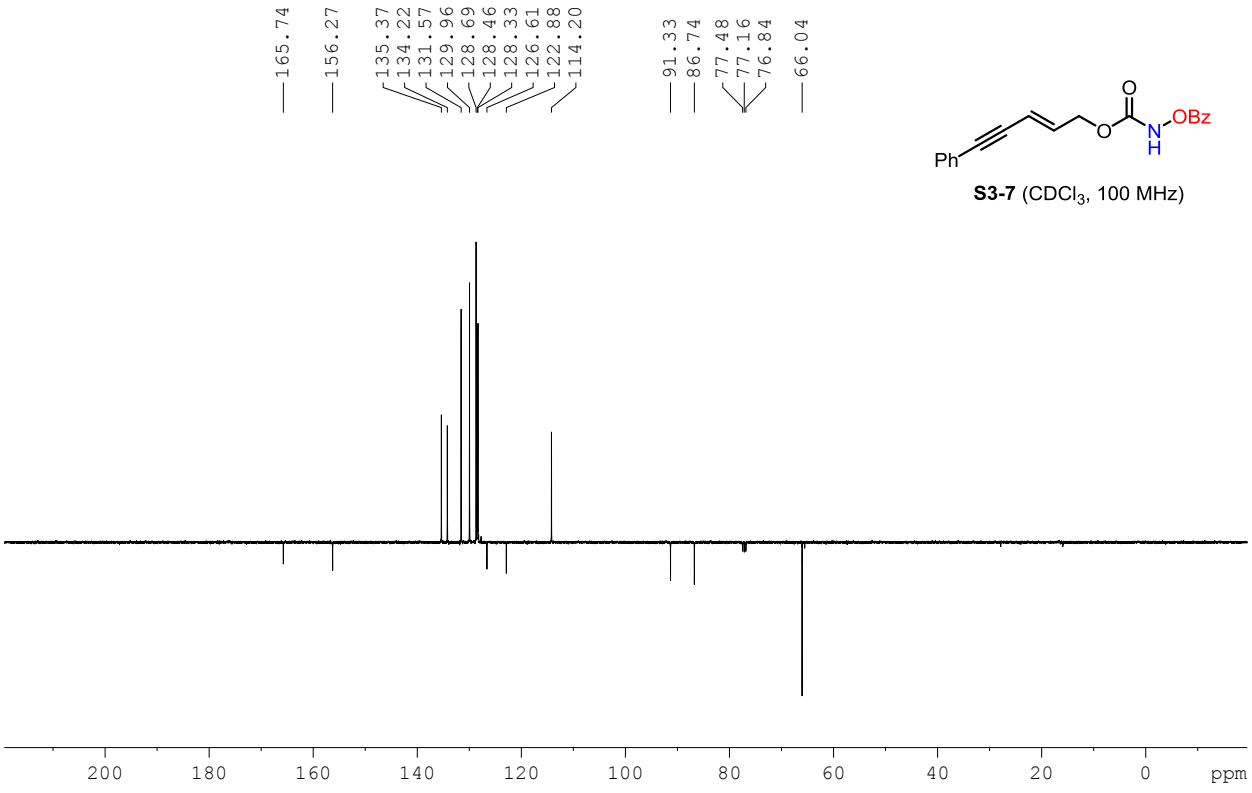

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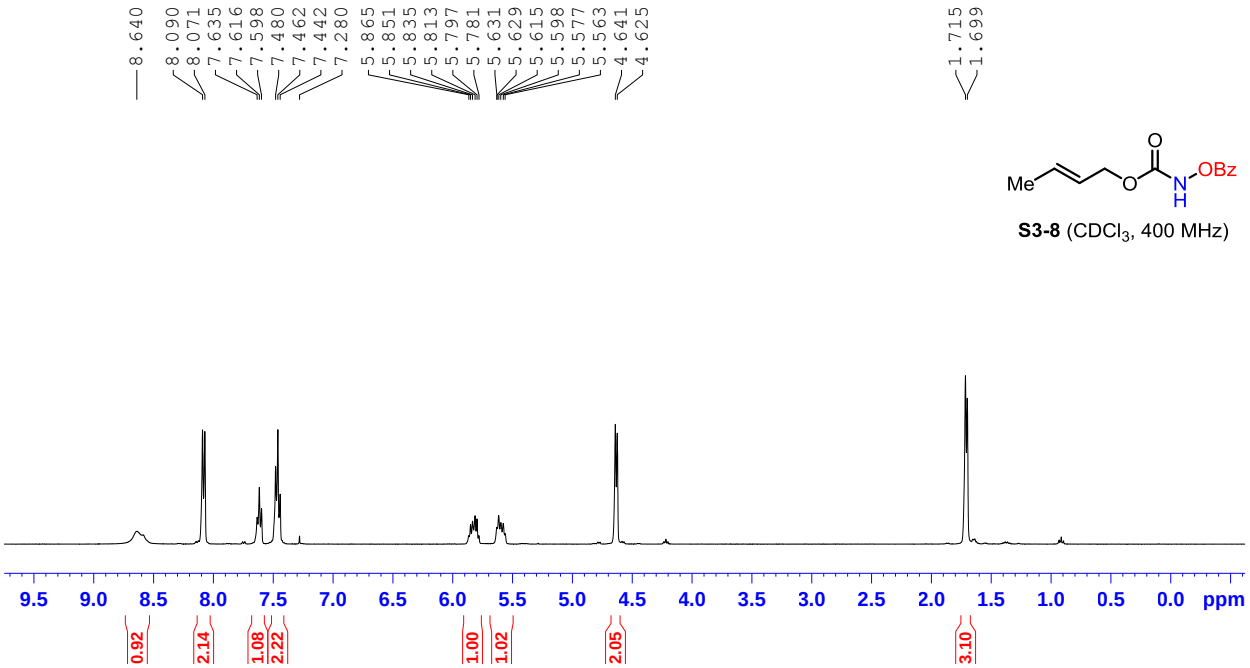

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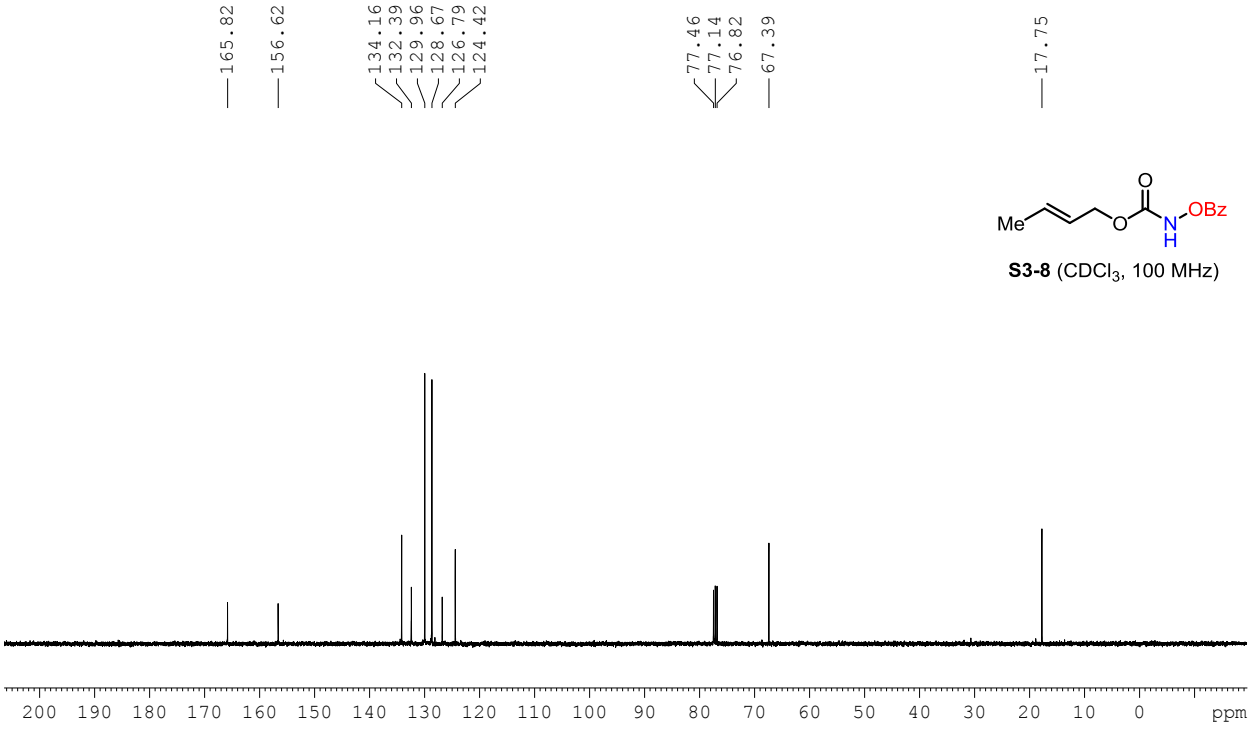

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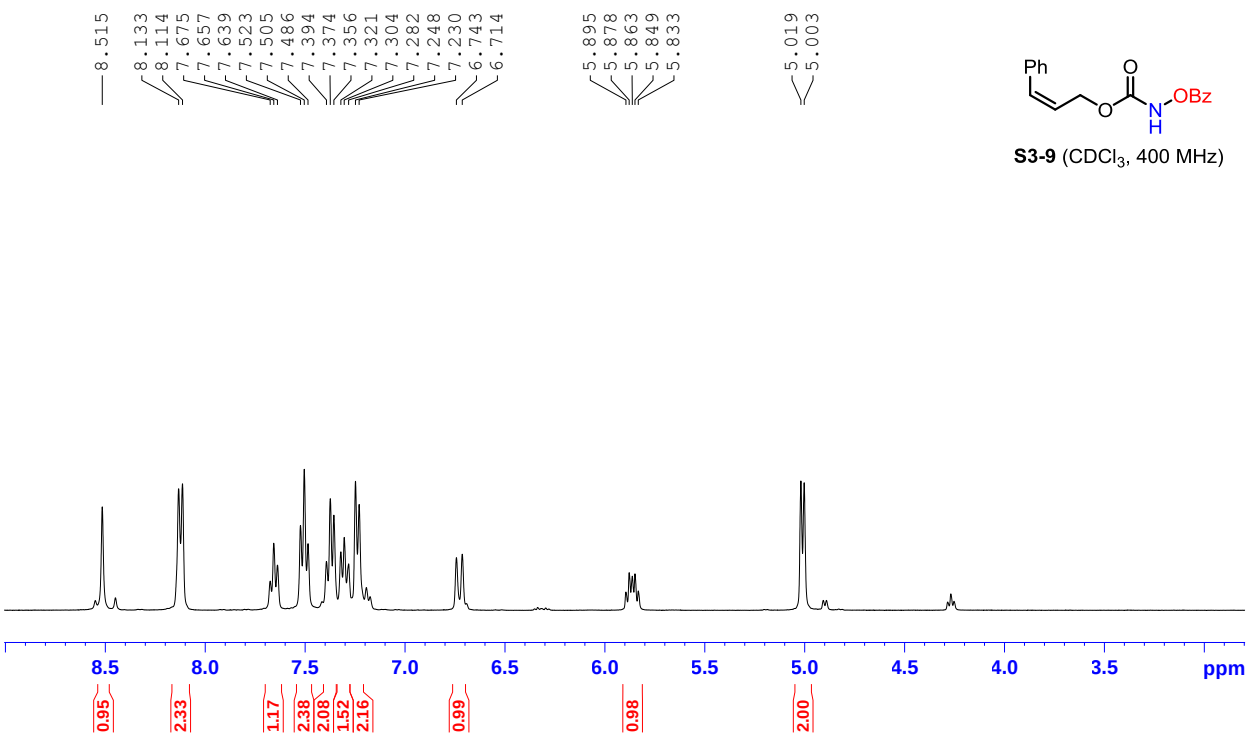

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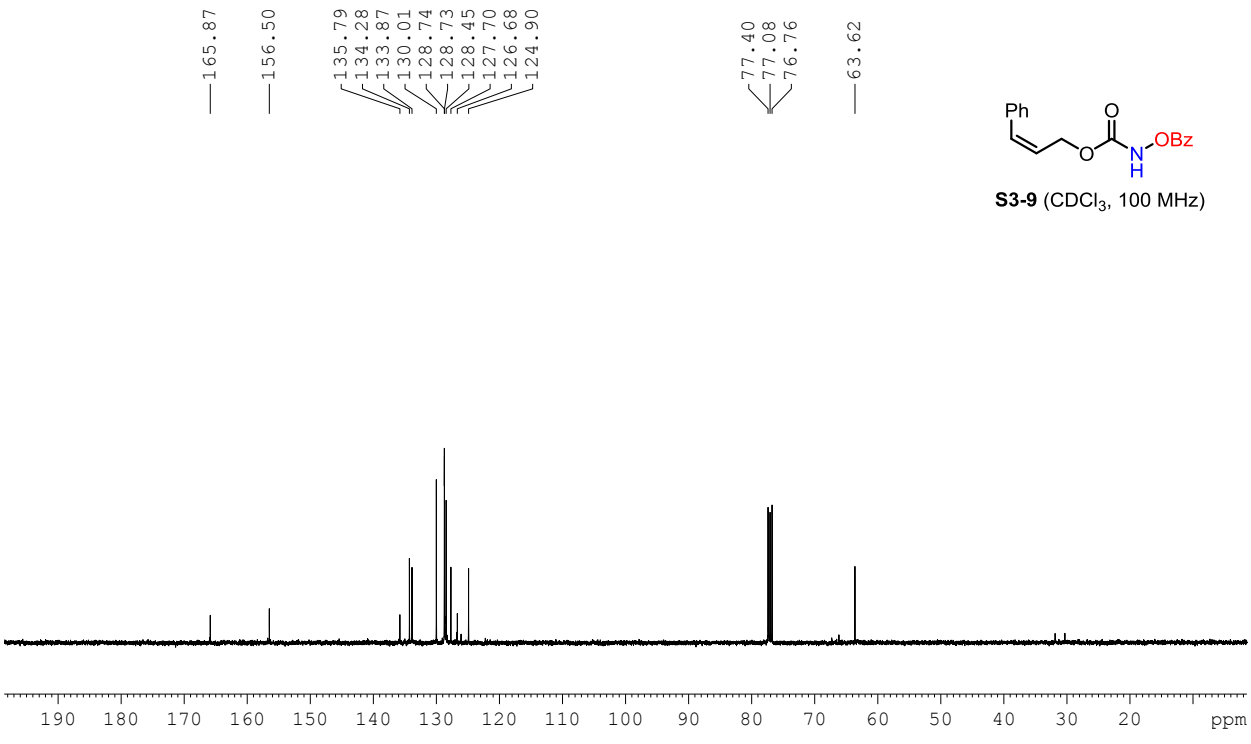
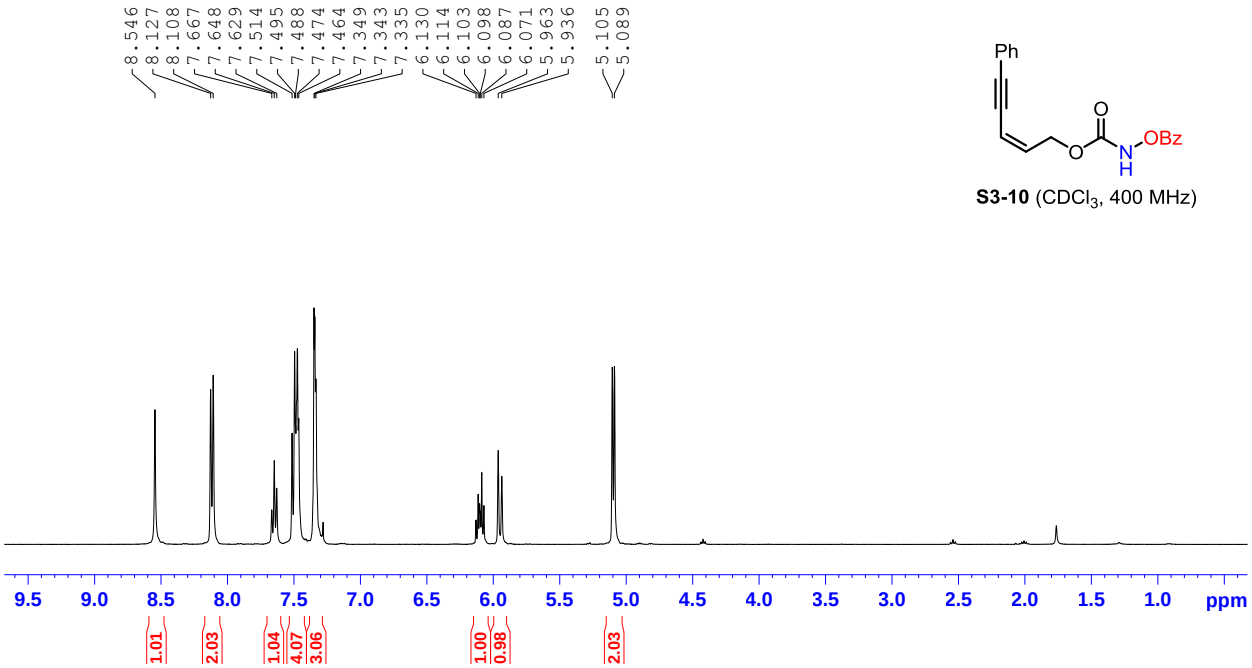


S3-9 ($CDCl_3$, 100 MHz)



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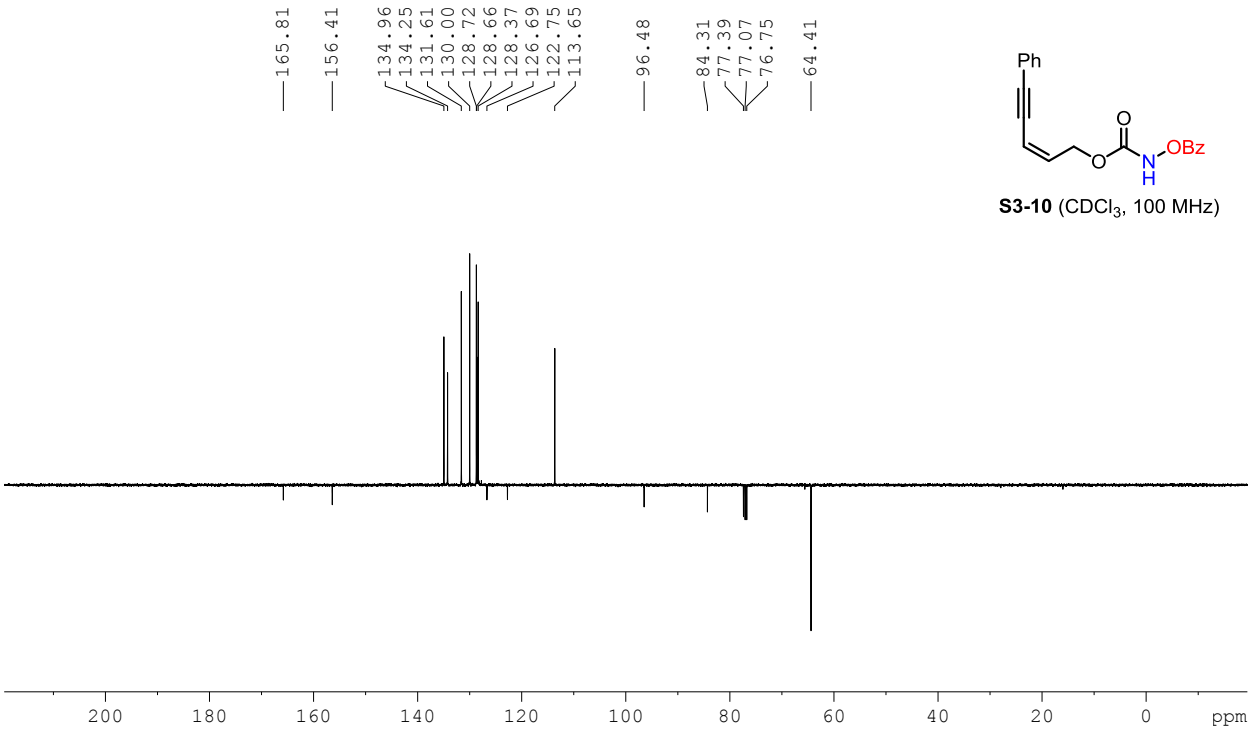

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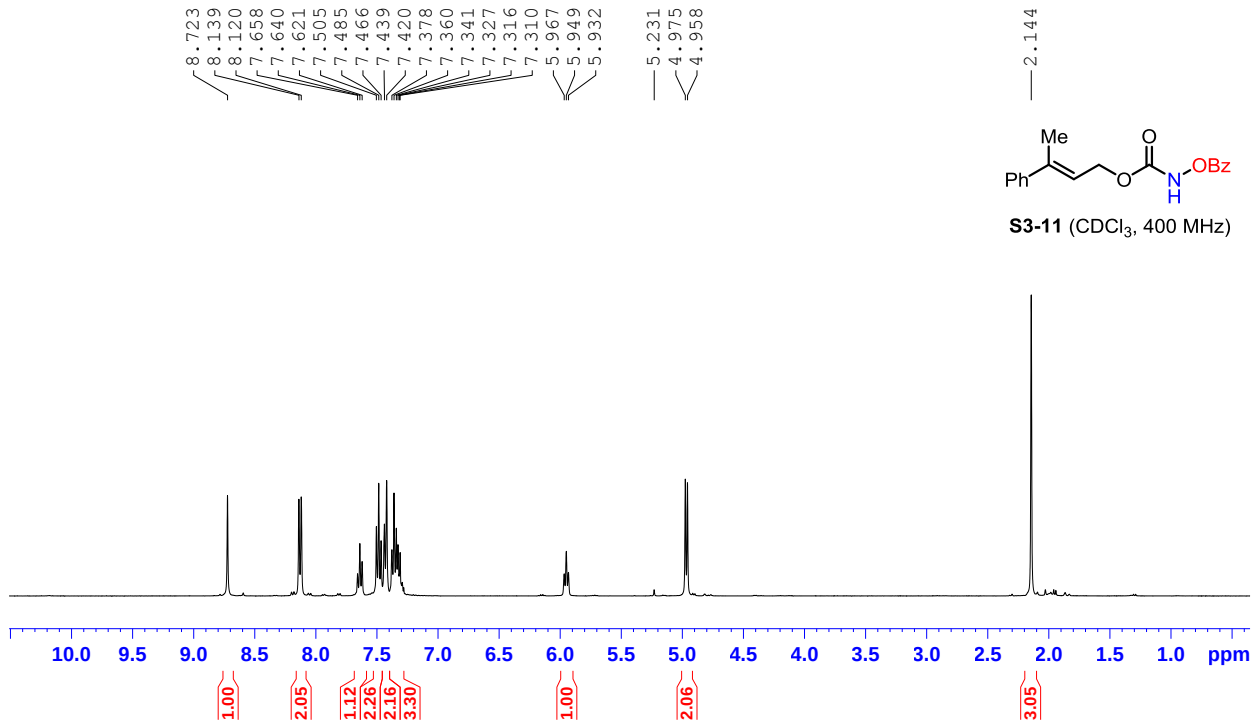

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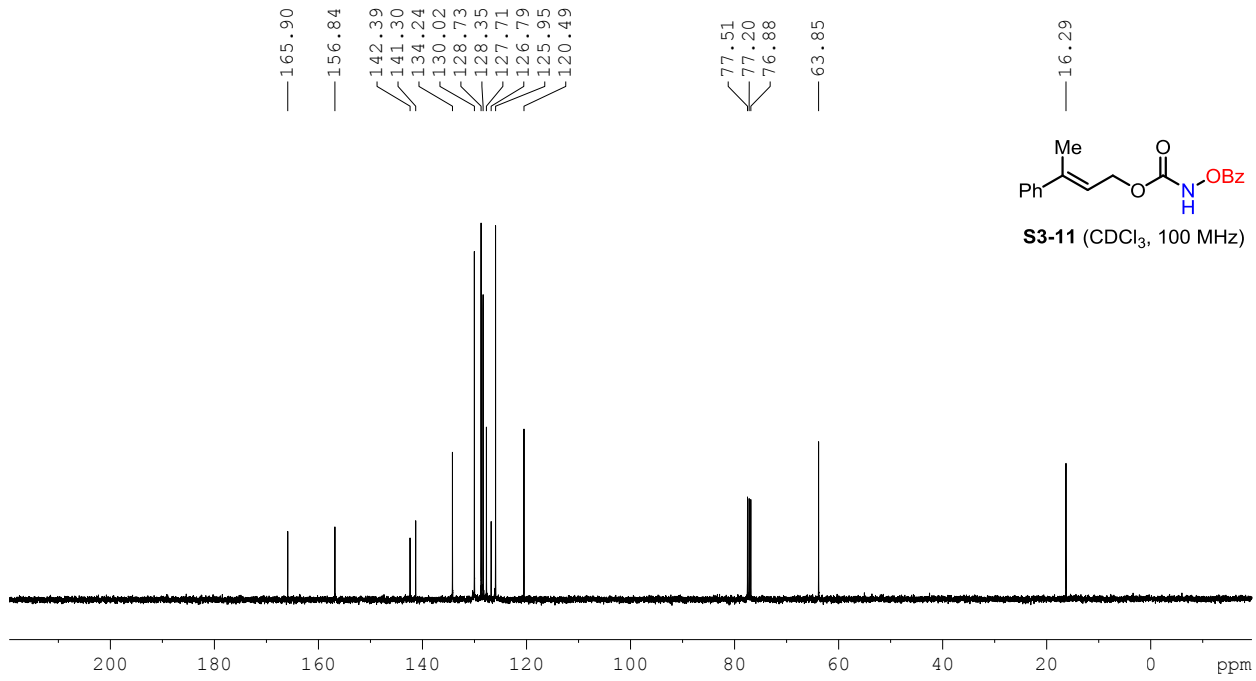
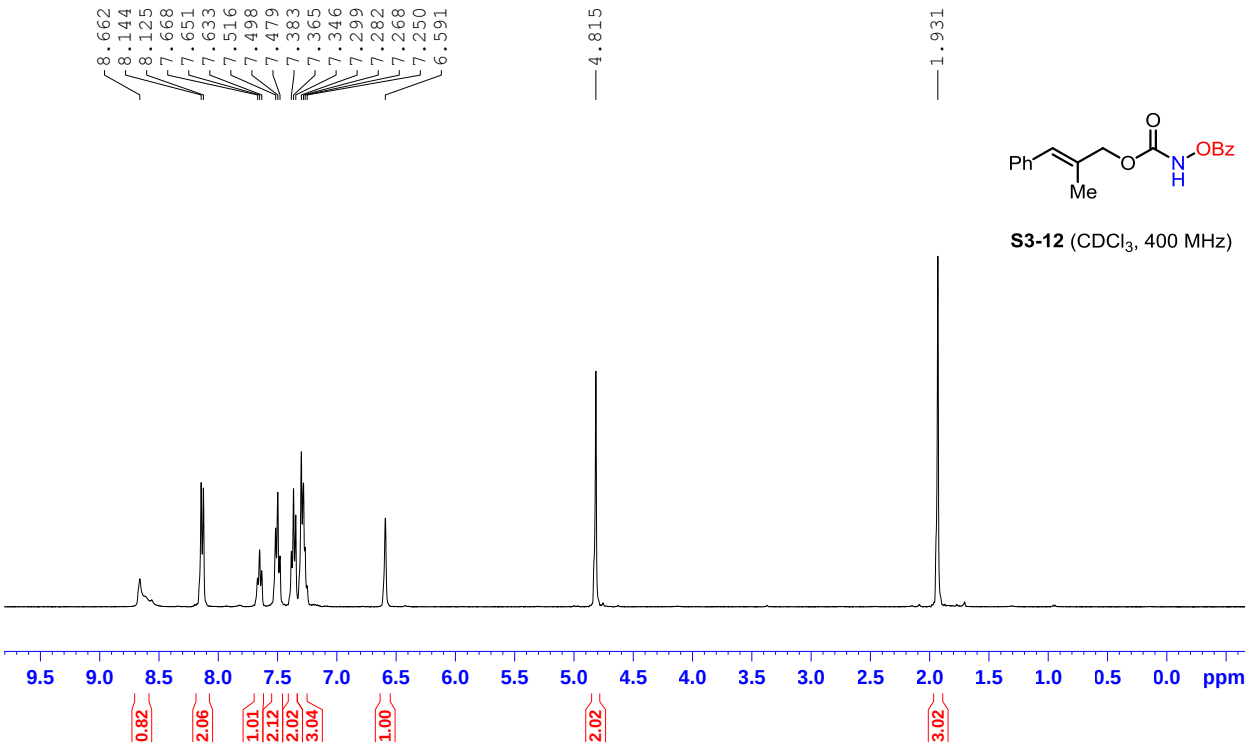


S3-11 ($CDCl_3$, 100 MHz)



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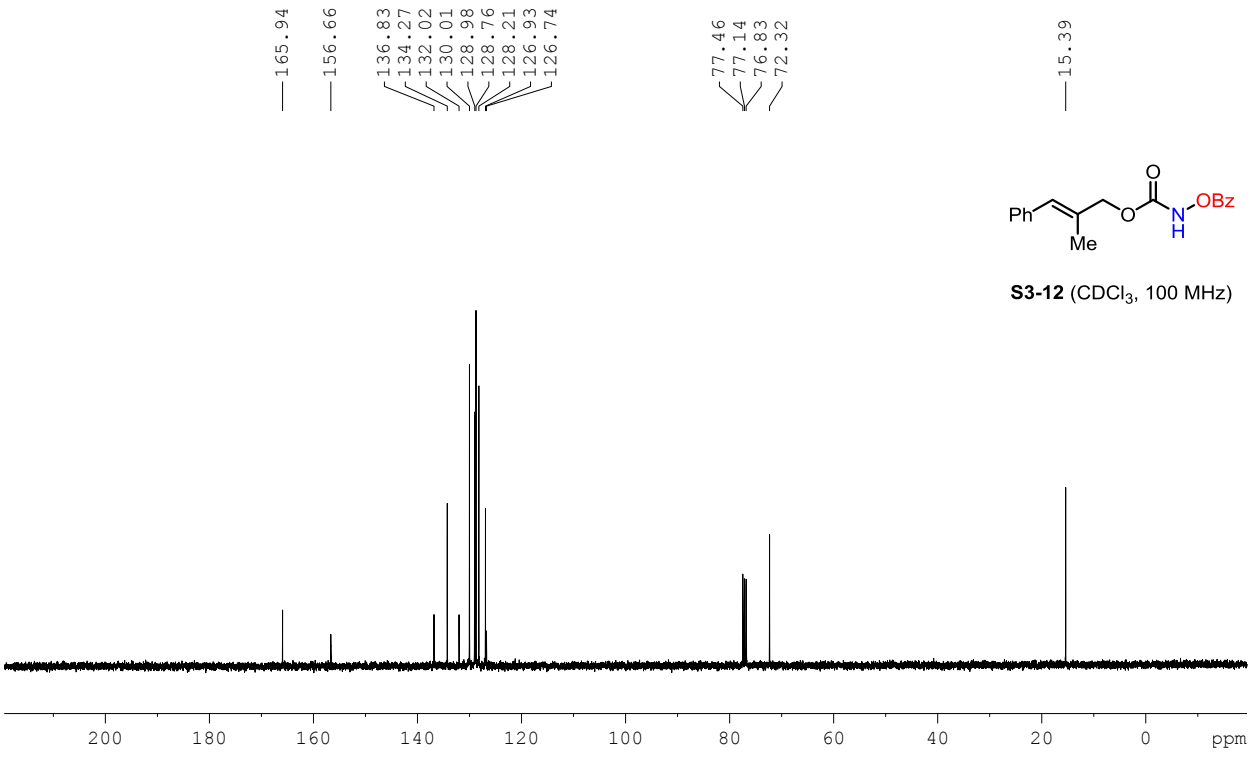
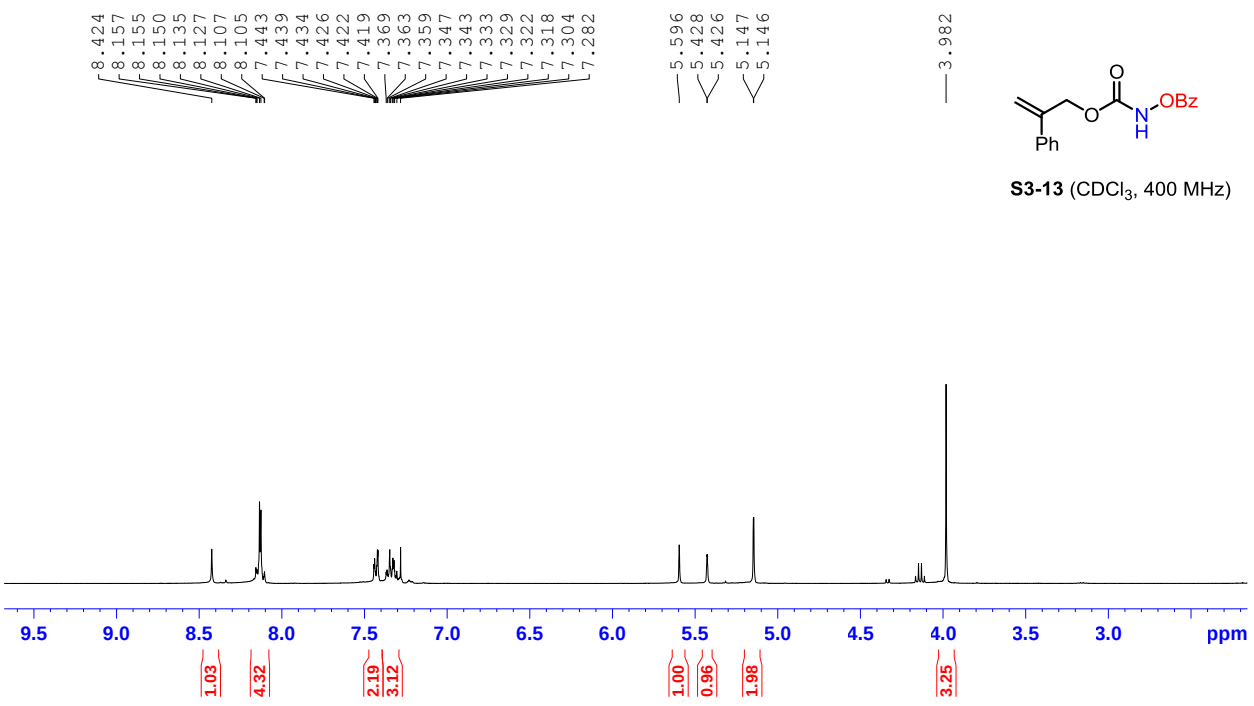
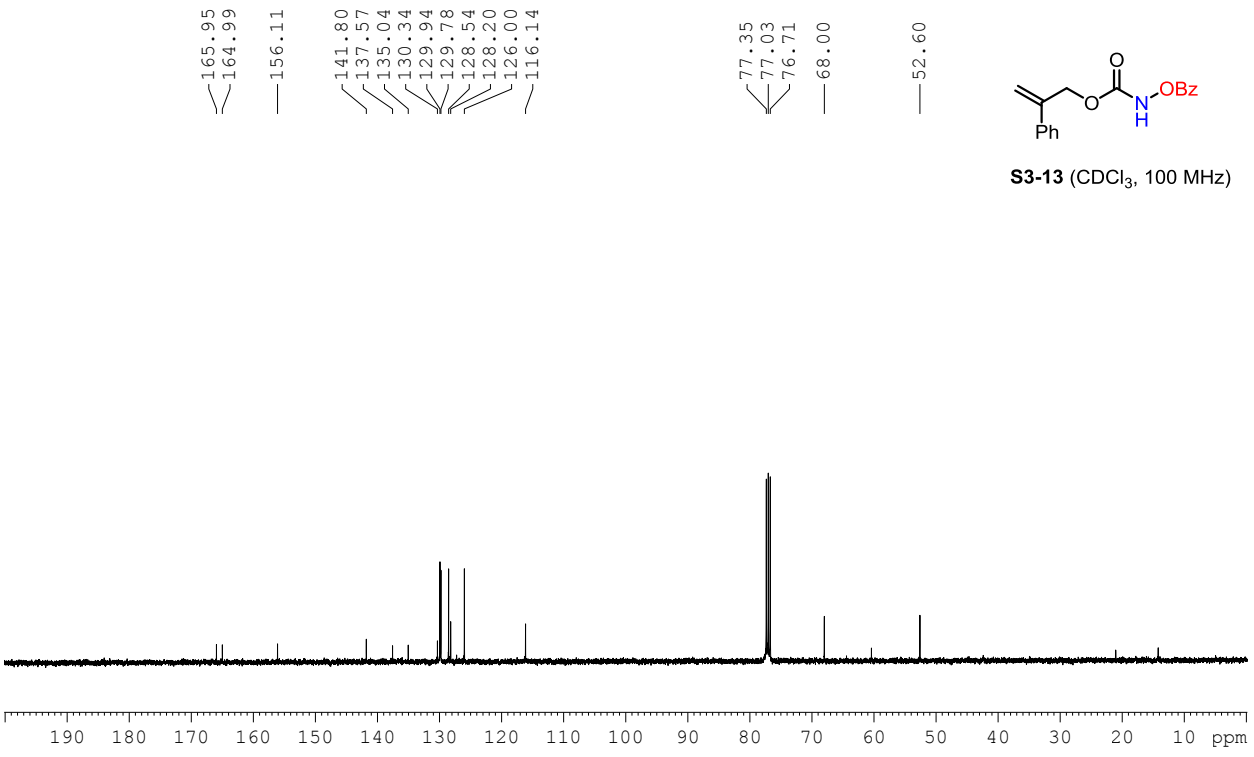


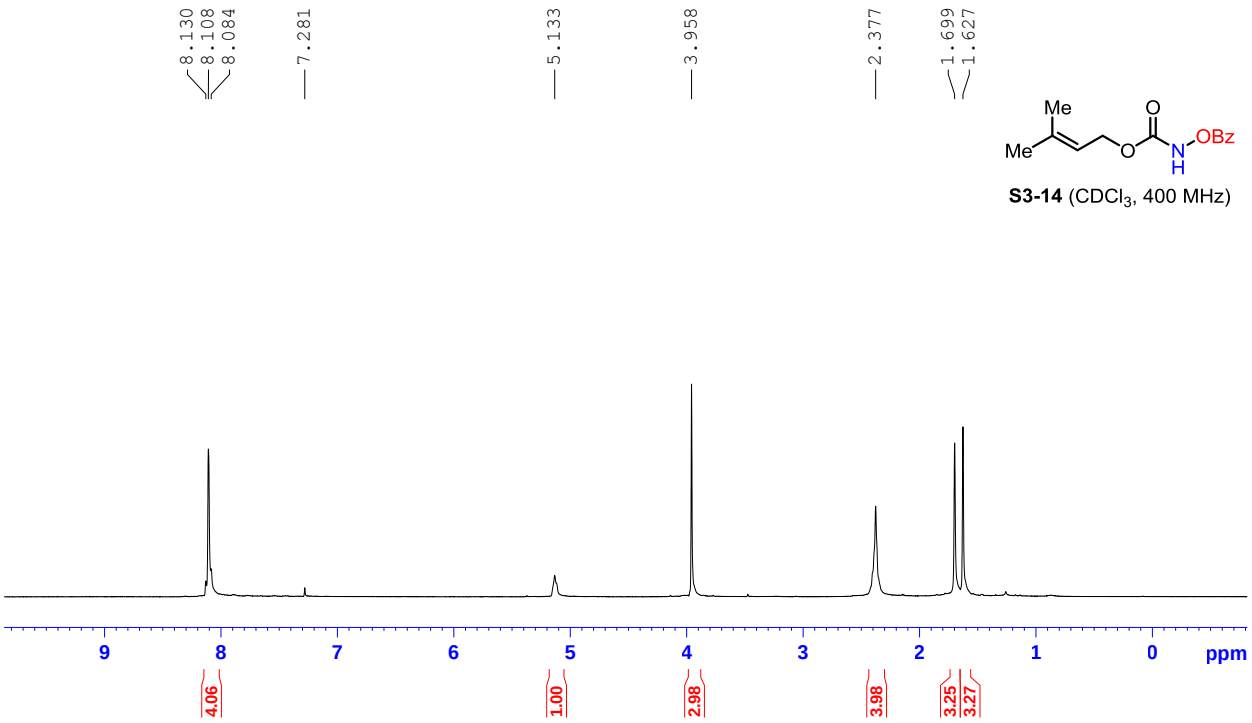
S3-12 ($CDCl_3$, 100 MHz)



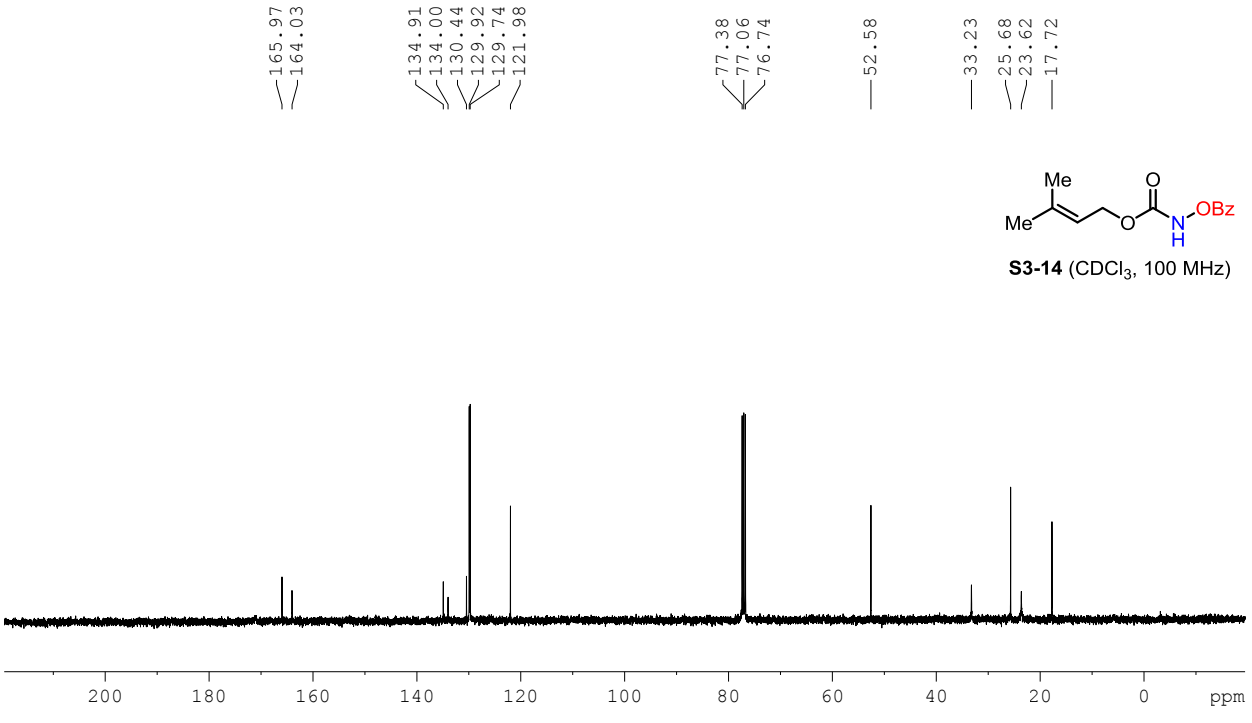
S3-13 ($CDCl_3$, 400 MHz)



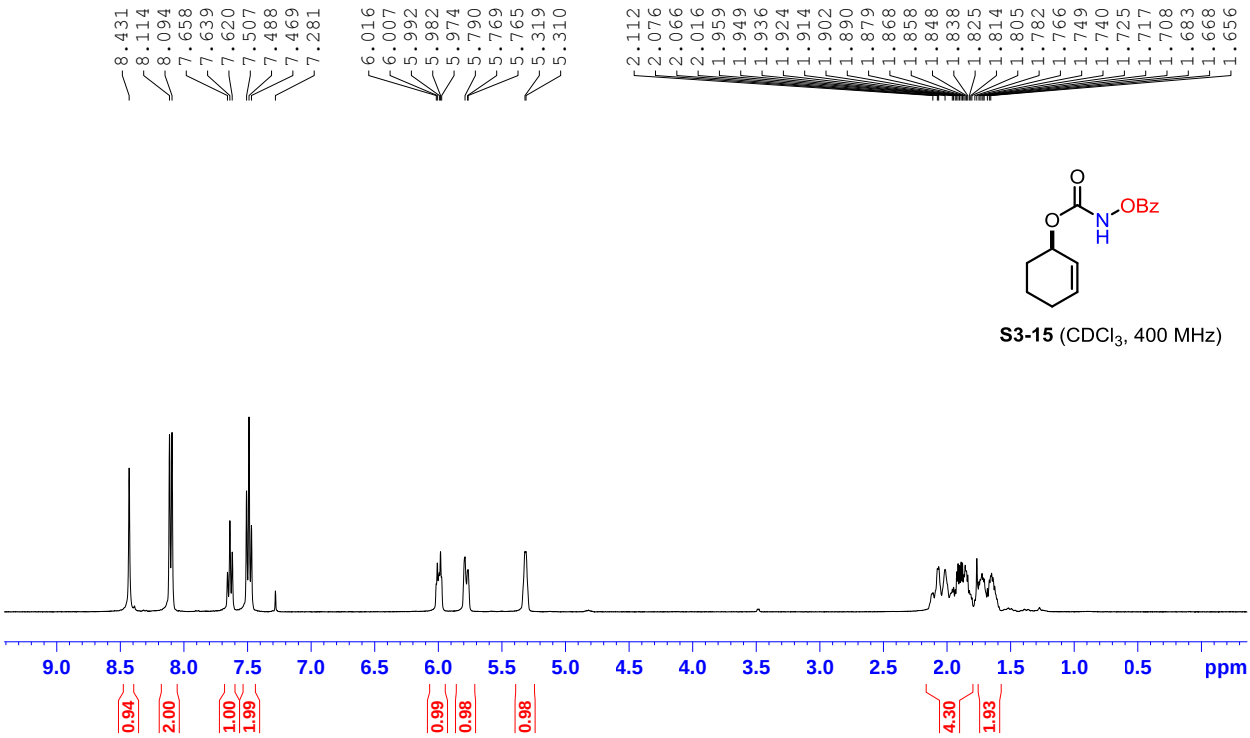
S3-13 ($CDCl_3$, 100 MHz)



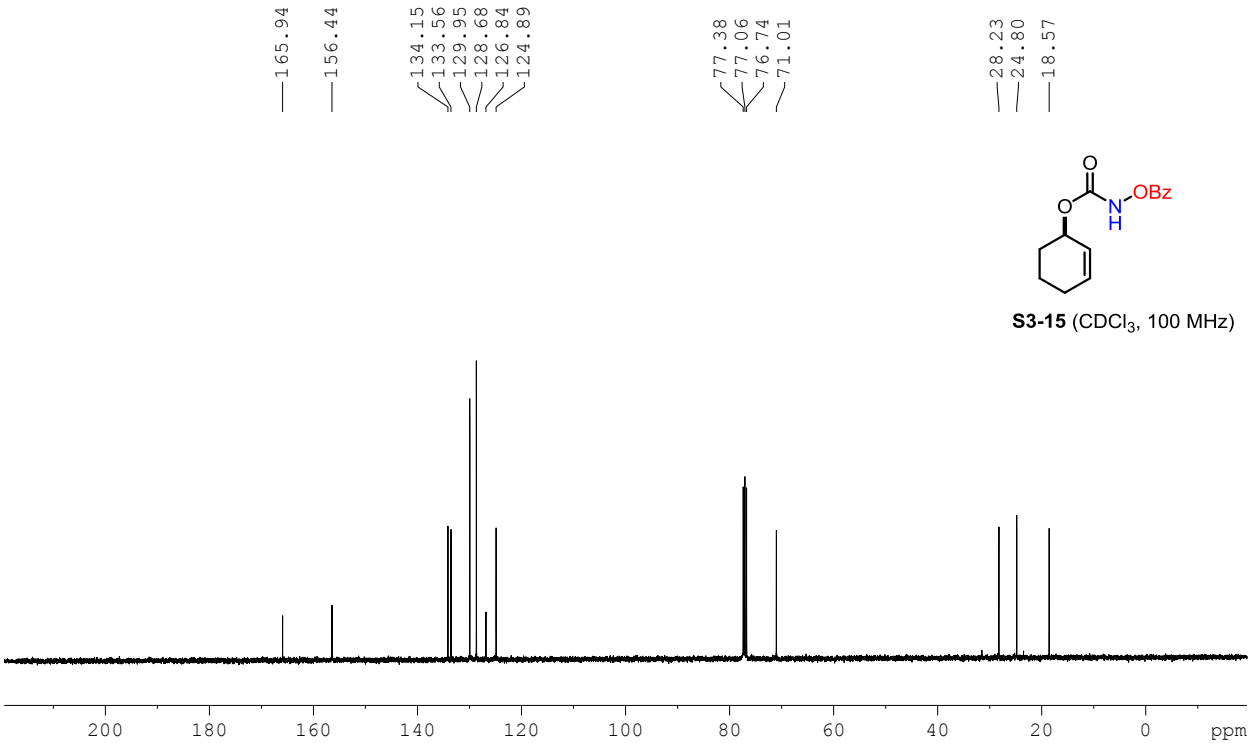
S3-14 ($CDCl_3$, 400 MHz)



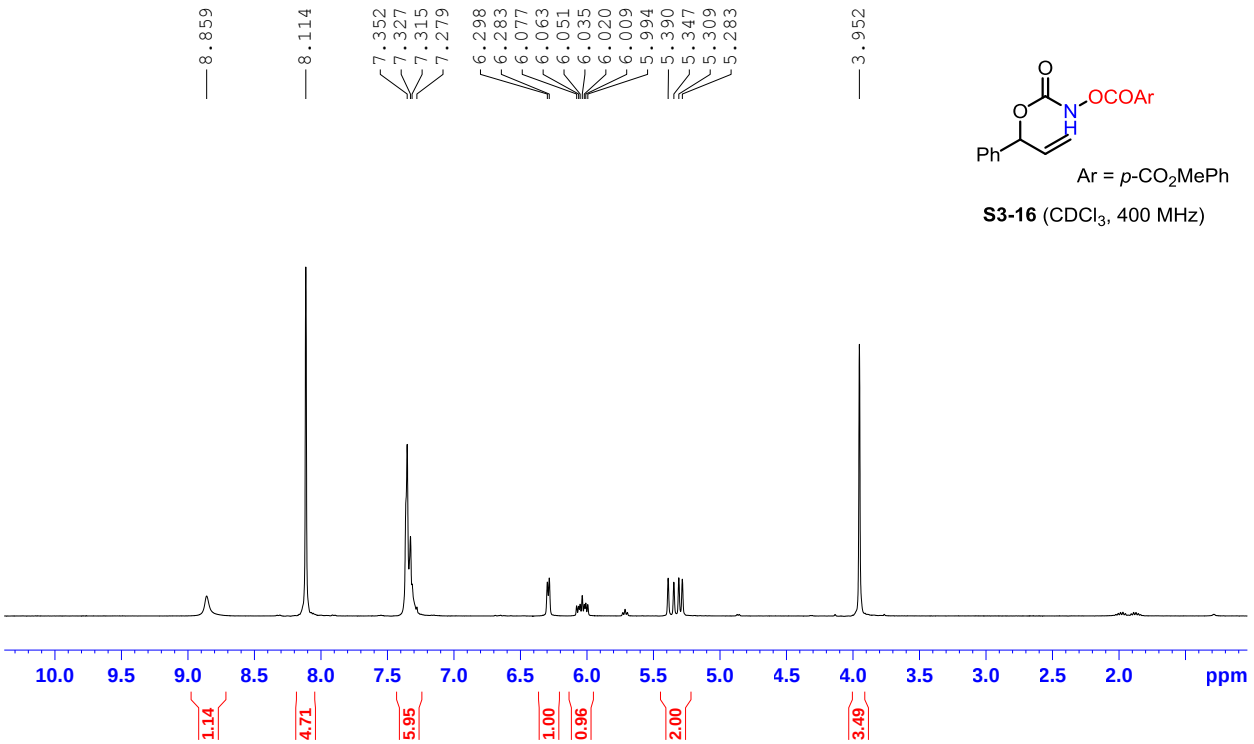
S3-14 ($CDCl_3$, 100 MHz)



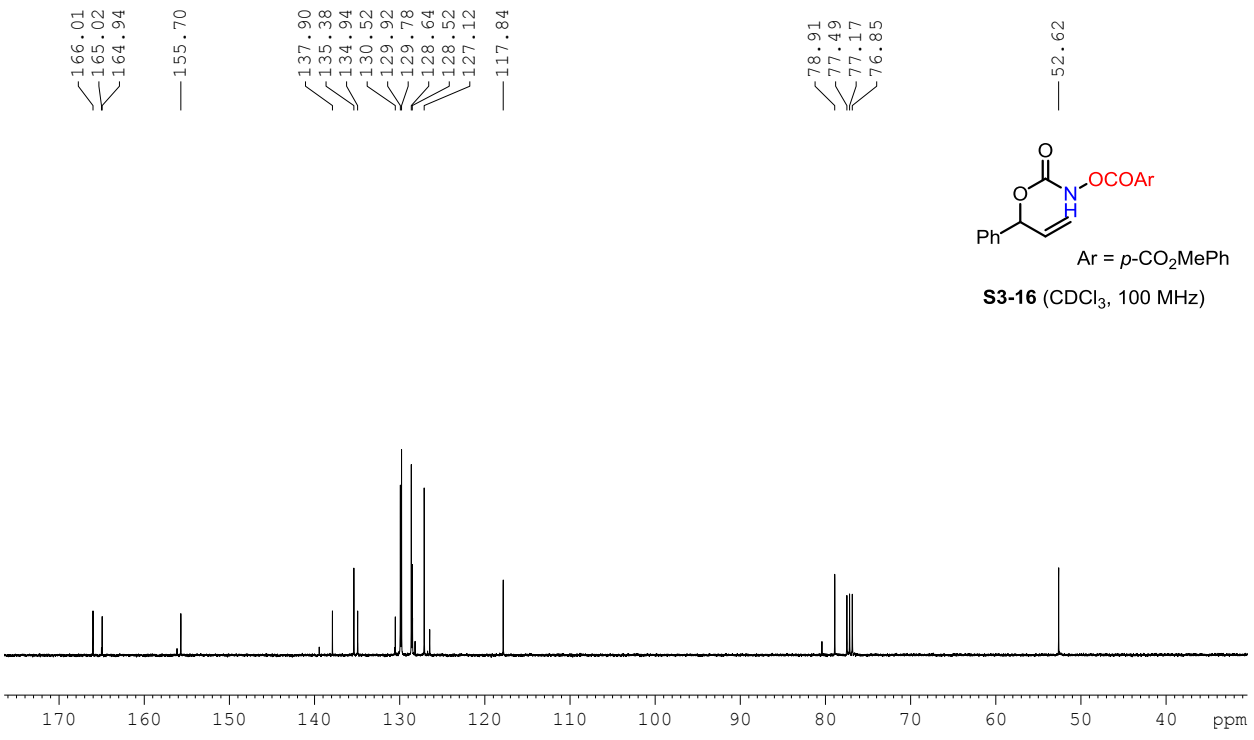
S3-15 ($CDCl_3$, 400 MHz)



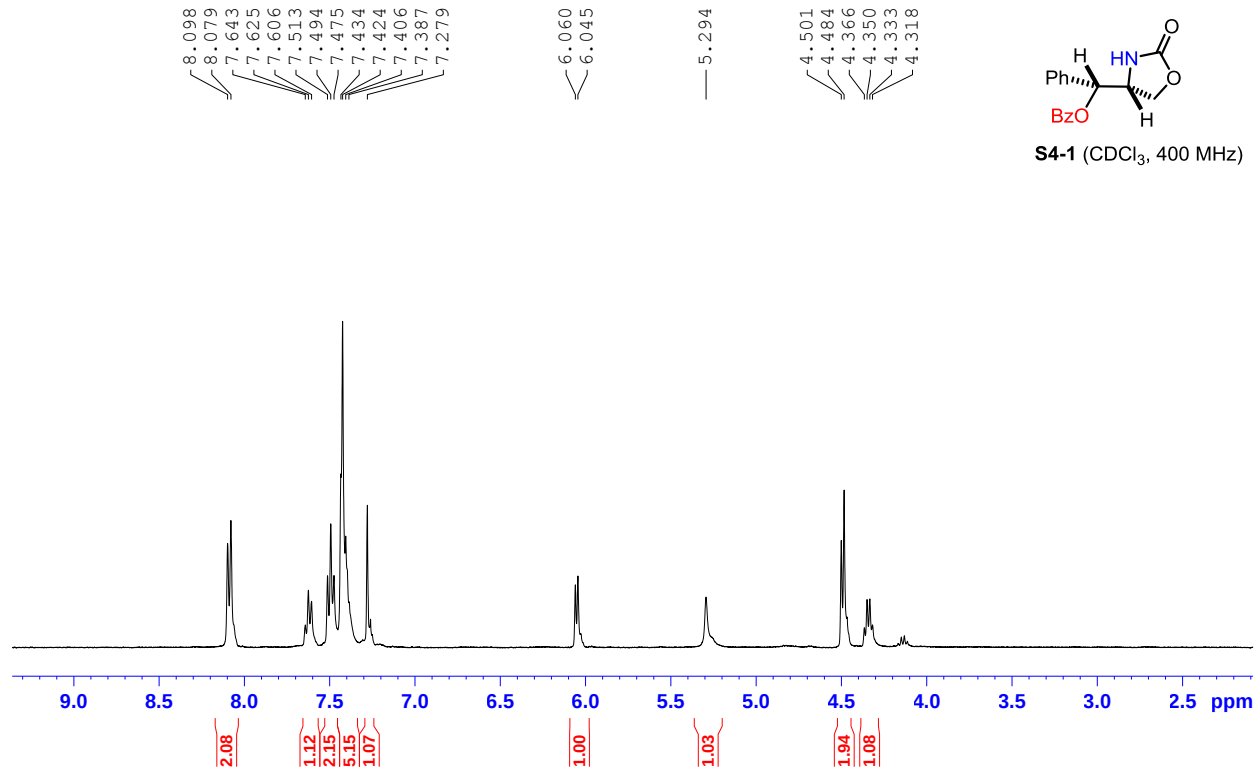
S3-15 ($CDCl_3$, 100 MHz)



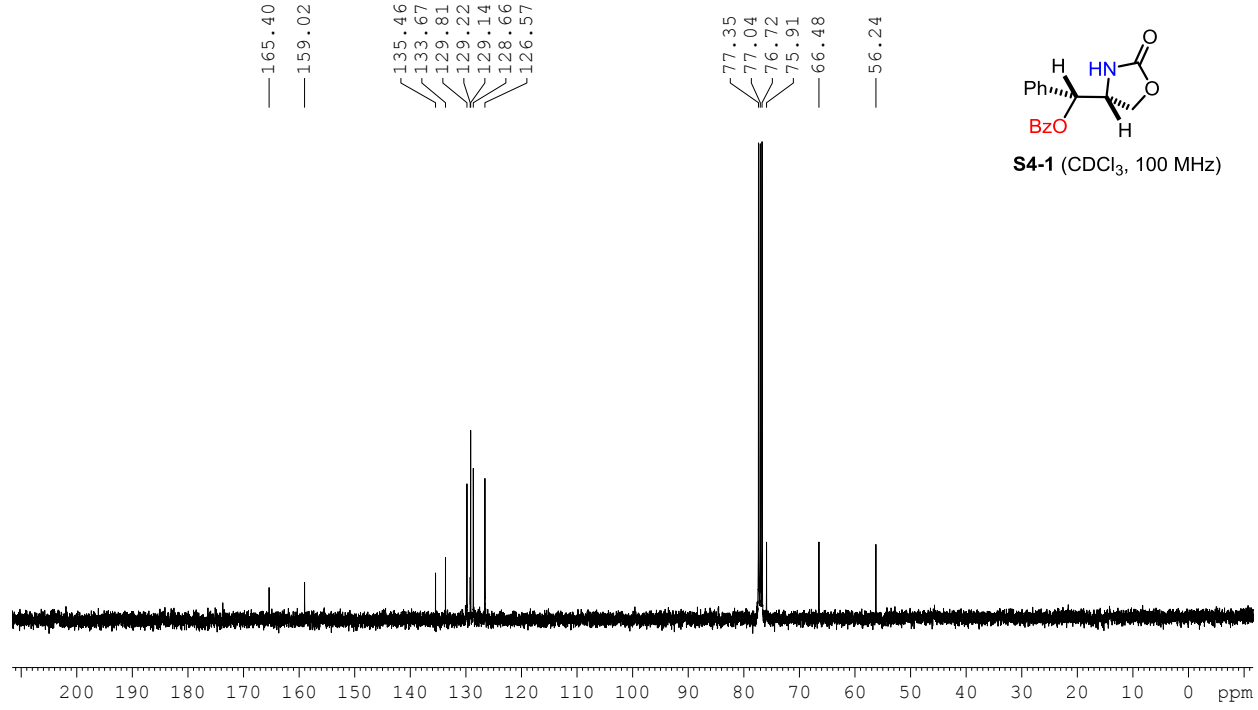
S3-16 ($CDCl_3$, 400 MHz)



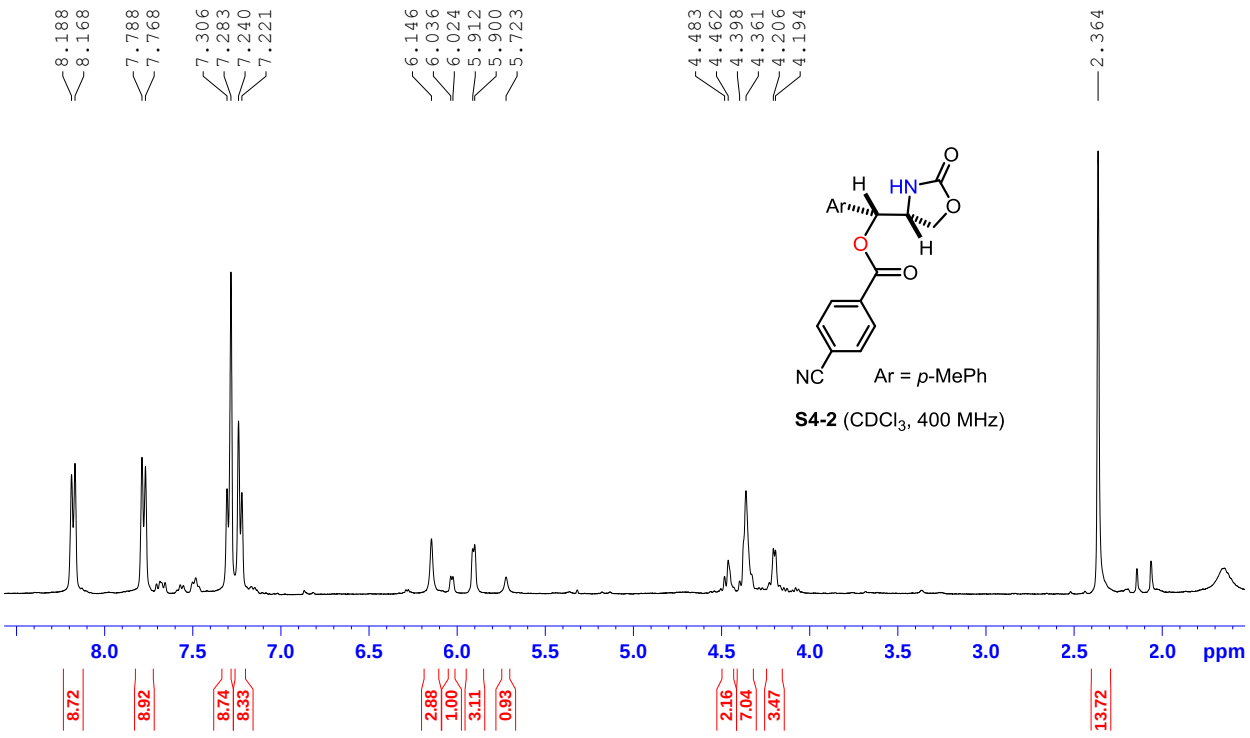
S3-16 ($CDCl_3$, 100 MHz)

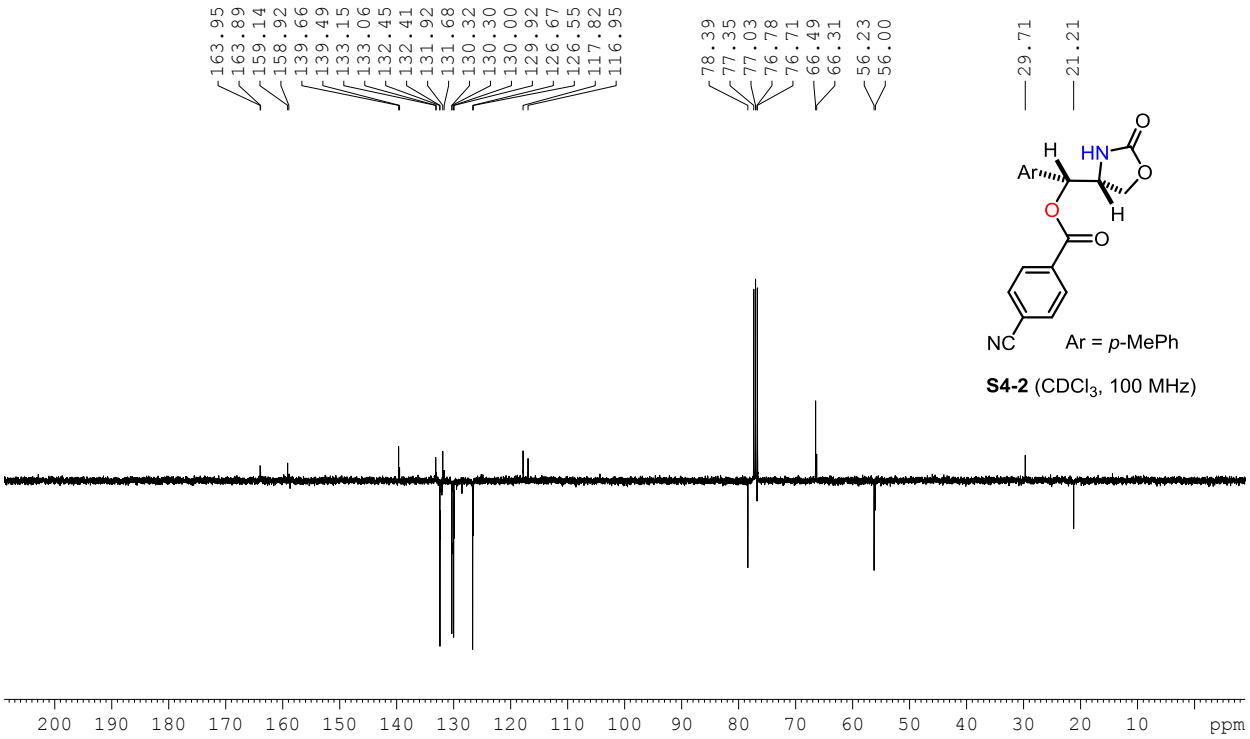


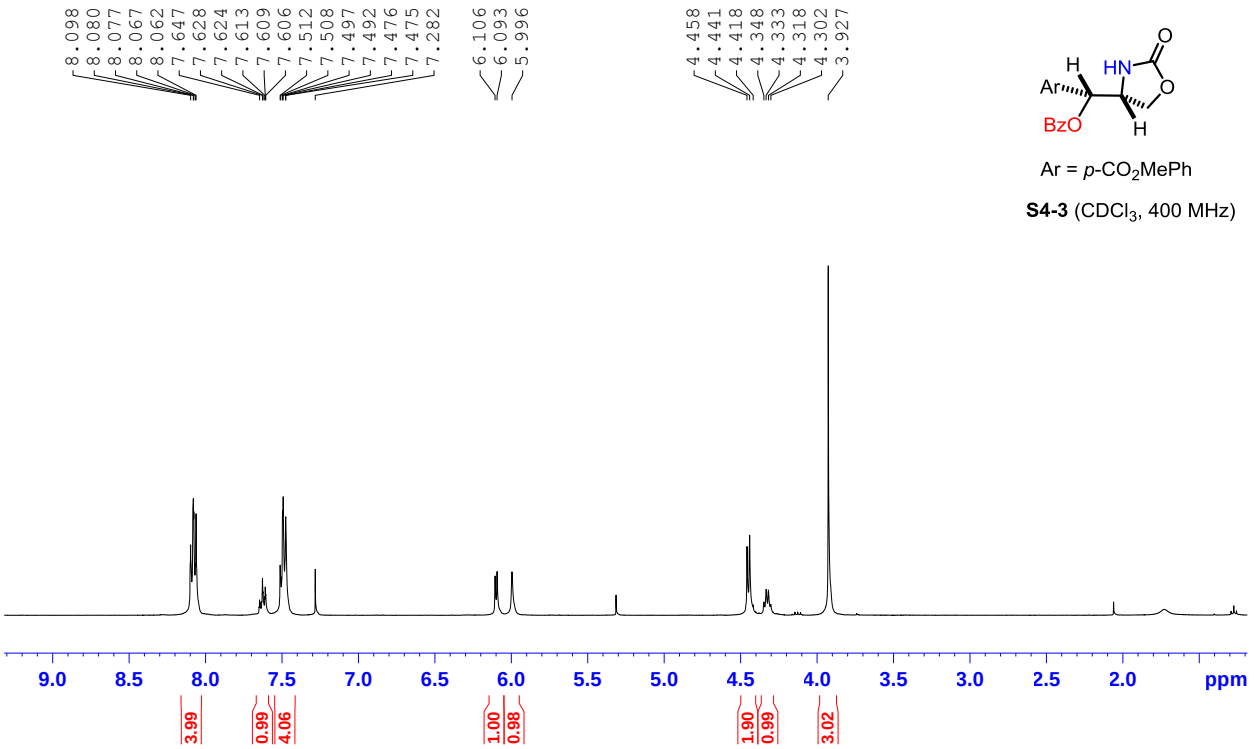
S4-1 ($CDCl_3$, 400 MHz)



S4-1 ($CDCl_3$, 100 MHz)

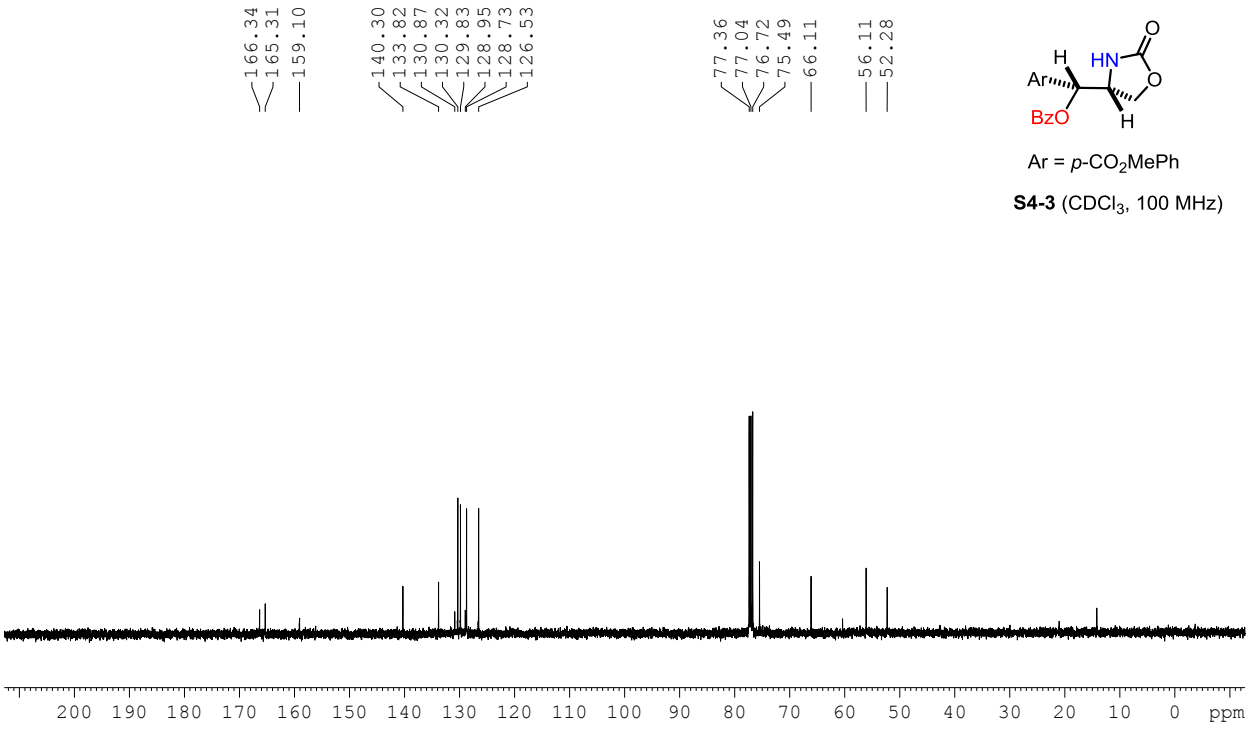

8.188
8.168
7.788
7.768
7.306
7.283
7.240
7.221
6.146
6.036
6.024
5.912
5.900
5.723
4.483
4.462
4.398
4.361
4.206
4.194
2.364
Ar = p-MePh
S4-2 (CDCl3, 400 MHz)
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 ppm
8.72
8.92
8.74
8.33
2.88
1.00
3.11
0.93
2.16
7.04
3.47
13.72


163.95
163.89
159.14
158.92
139.66
139.49
133.15
133.06
132.45
132.41
131.92
131.68
130.32
130.30
130.00
129.92
126.67
126.55
117.82
116.95
78.39
77.35
77.03
76.78
76.71
66.49
66.31
56.23
56.00
29.71
21.21
Ar = p-MePh
S4-2 (CDCl3, 100 MHz)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



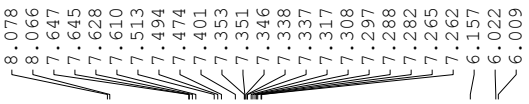
Ar = *p*-CO_2MePh

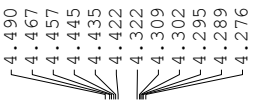
S4-3 ($CDCl_3$, 400 MHz)

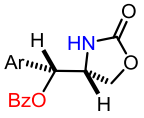


Ar = *p*-CO_2MePh

S4-3 ($CDCl_3$, 100 MHz)

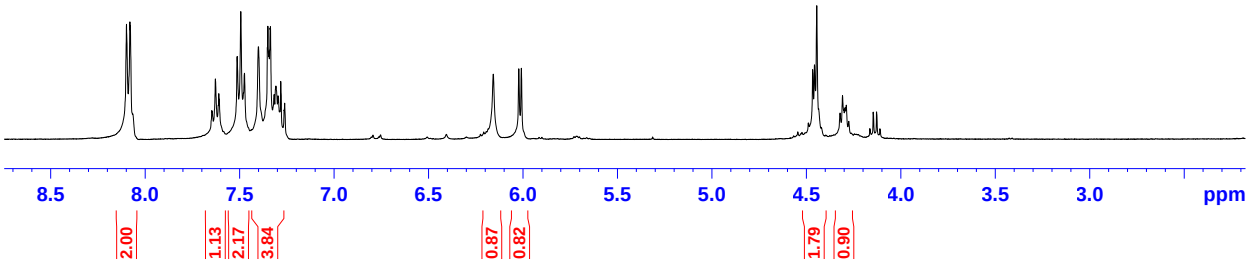


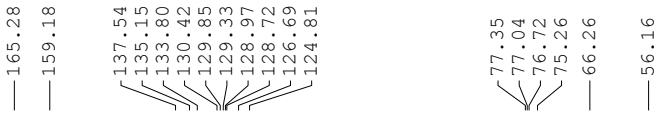


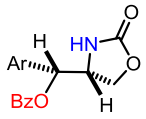


Ar = 3-ClPh

S4-4 ($CDCl_3$, 400 MHz)

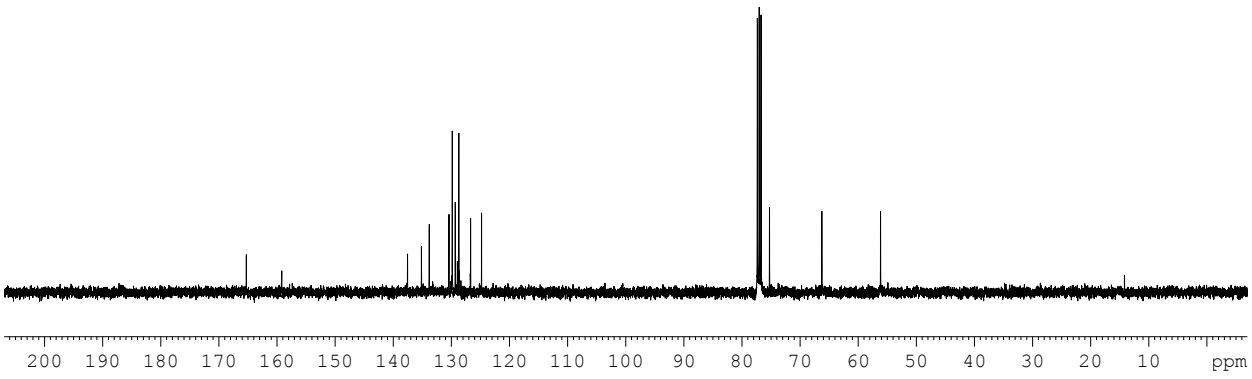


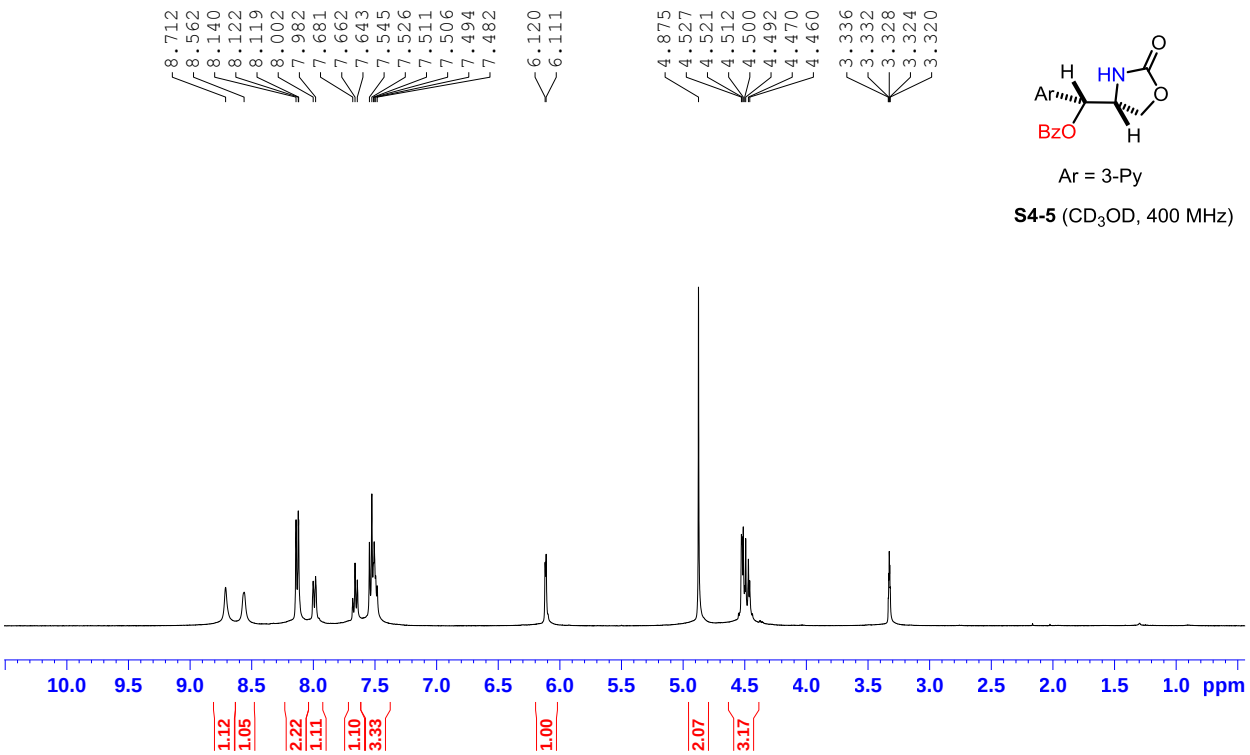




Ar = 3-ClPh

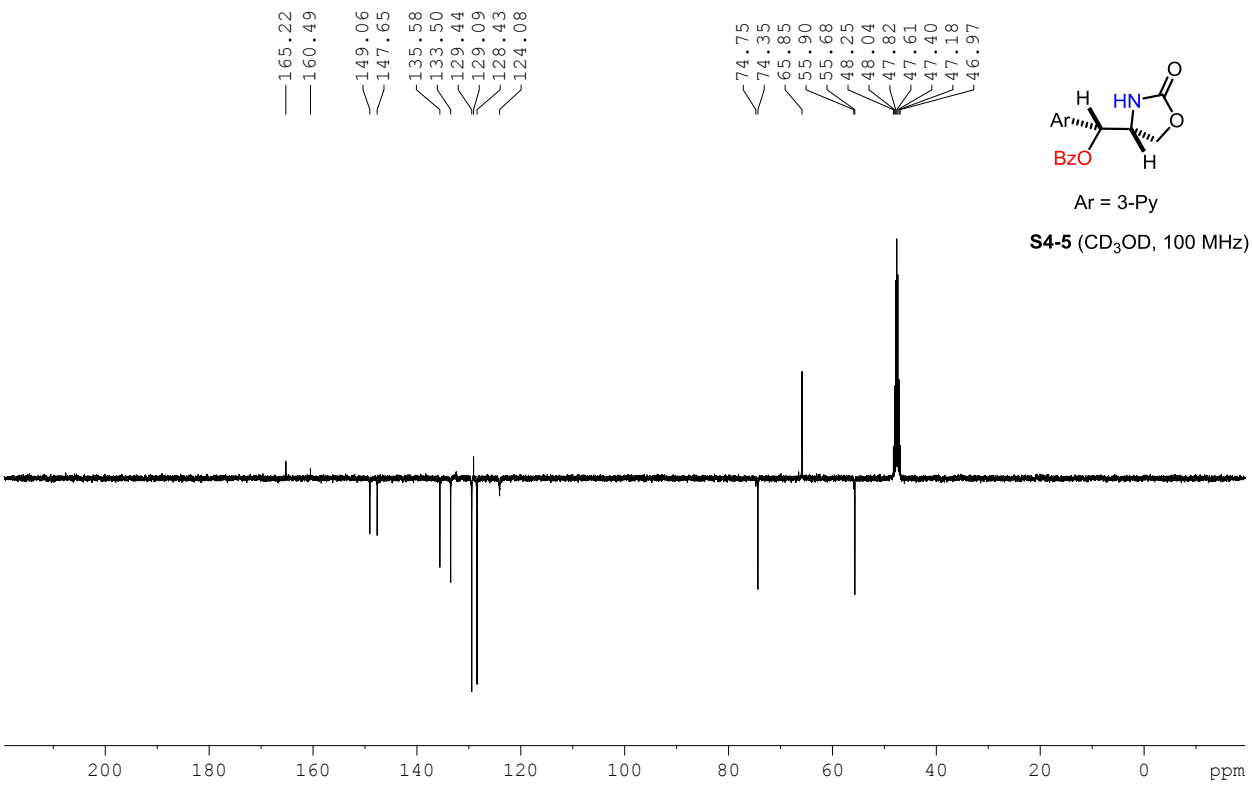
S4-4 ($CDCl_3$, 100 MHz)





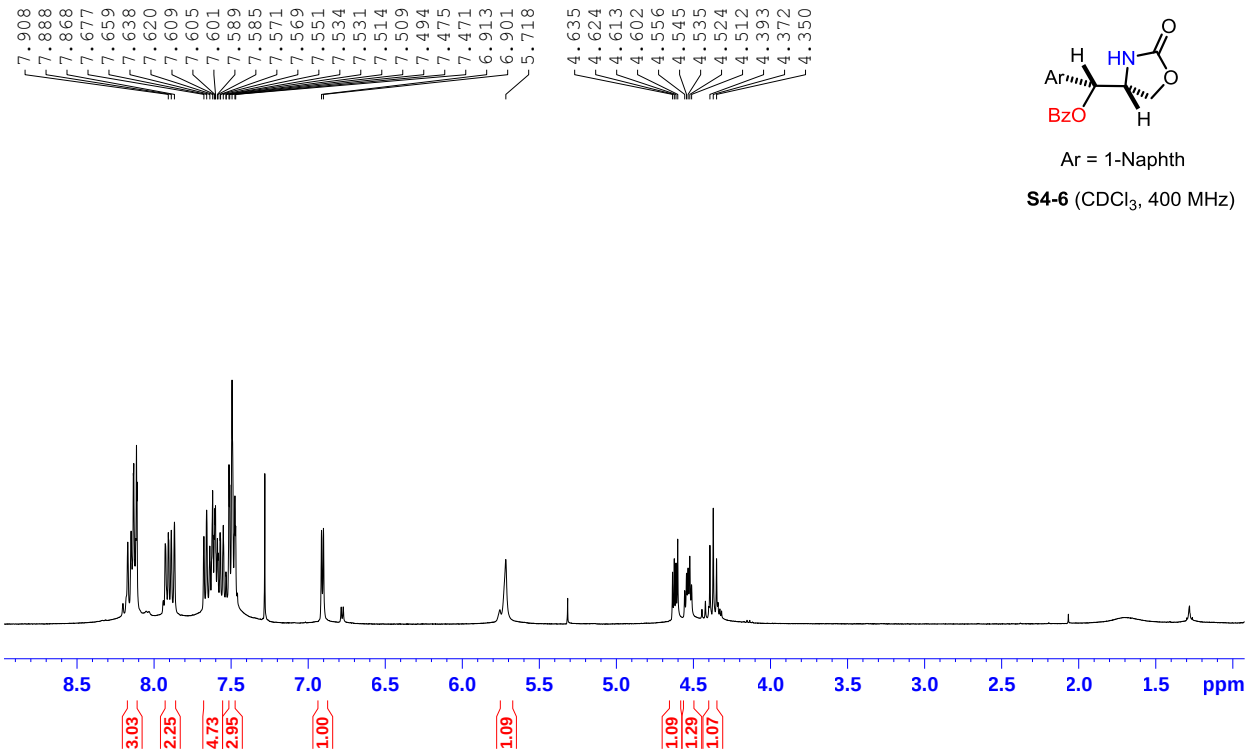
Ar = 3-Py

S4-5 (CD_3OD, 400 MHz)



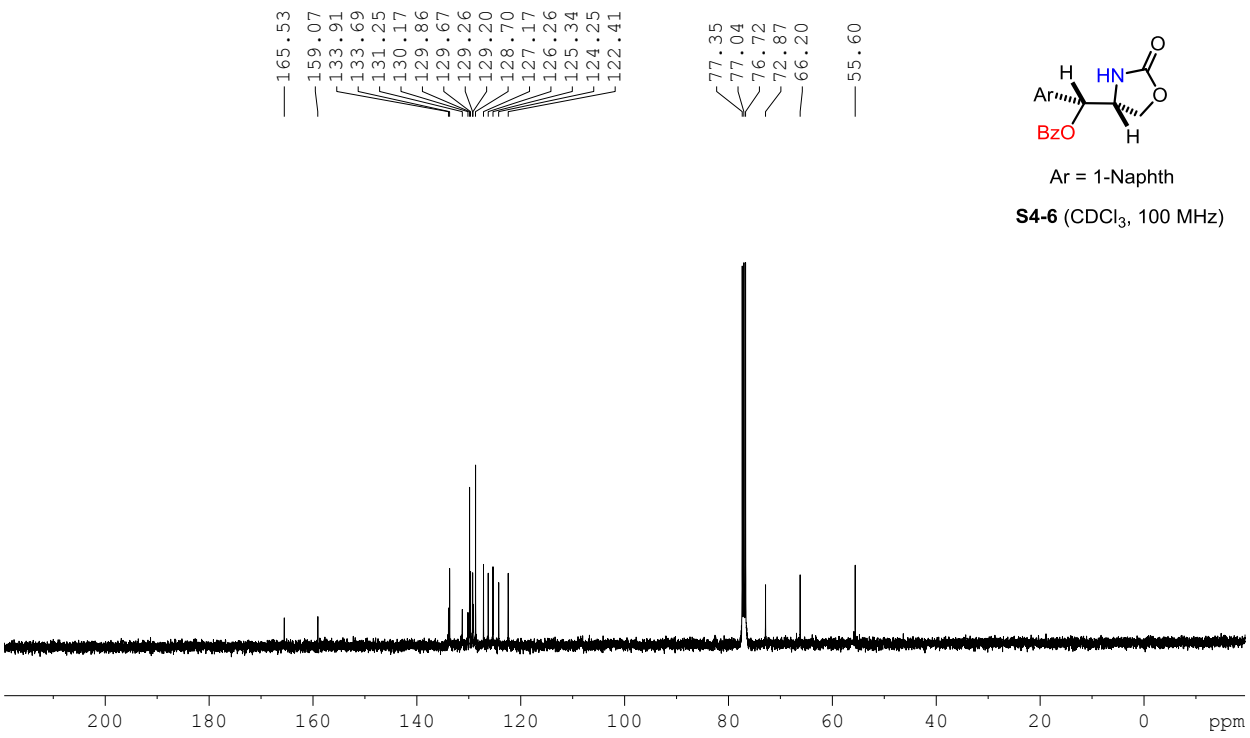
Ar = 3-Py

S4-5 (CD_3OD, 100 MHz)



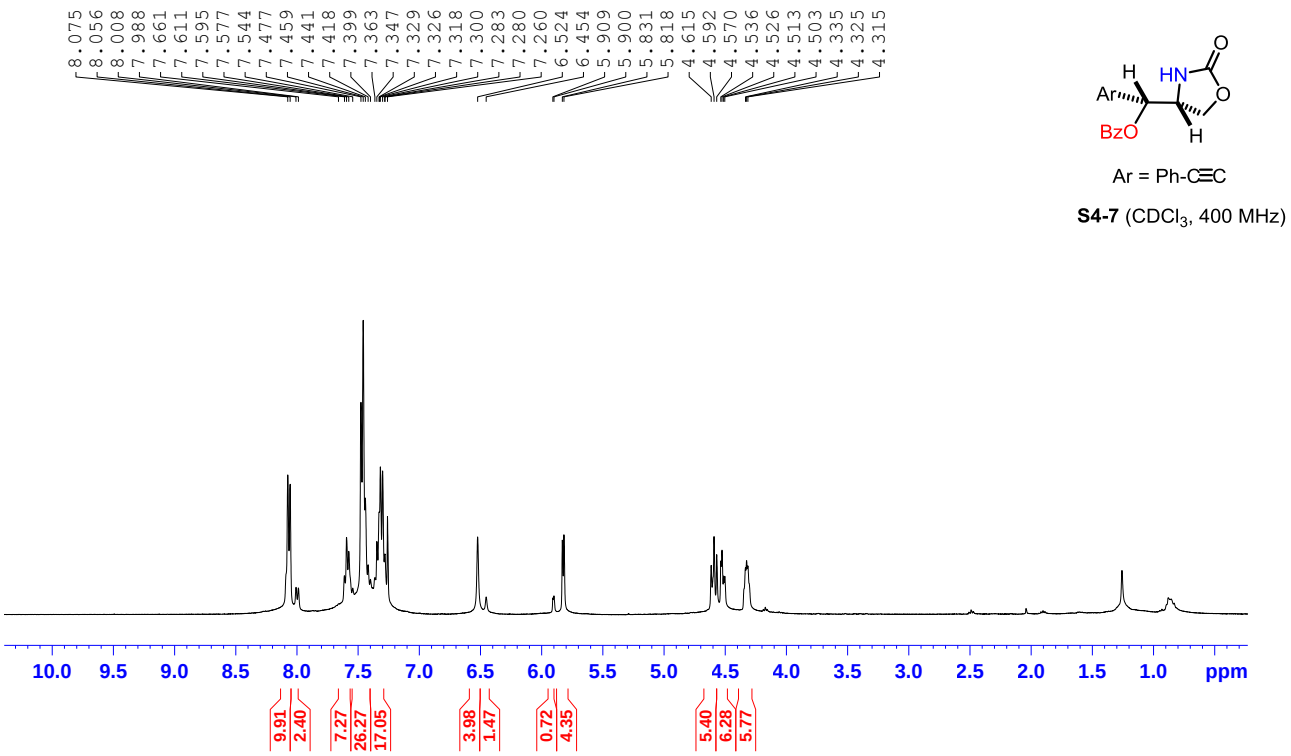
Ar = 1-Naphth

S4-6 ($CDCl_3$, 400 MHz)



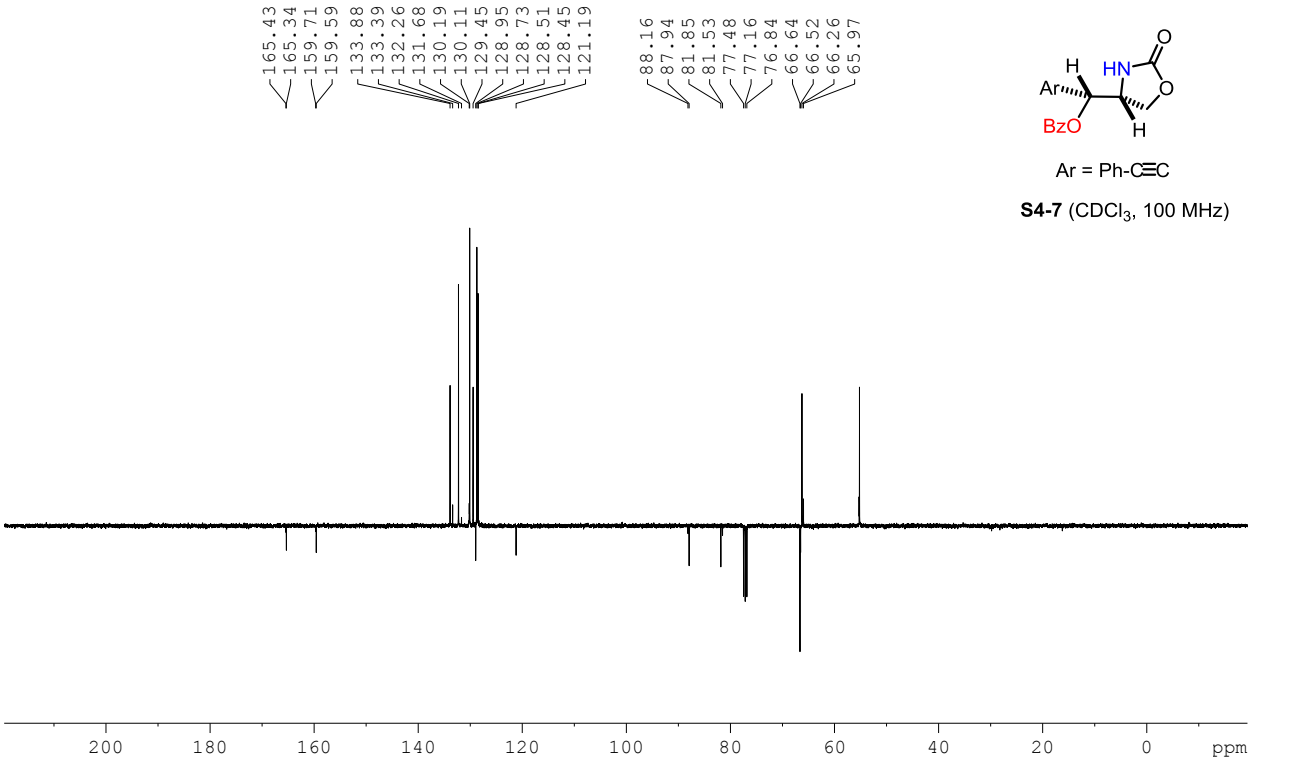
Ar = 1-Naphth

S4-6 ($CDCl_3$, 100 MHz)



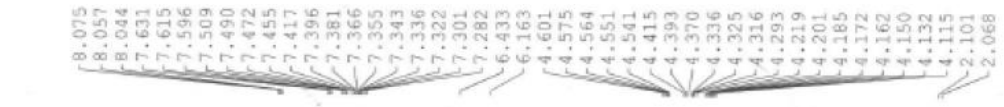
Ar = Ph-C≡C

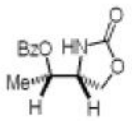
S4-7 ($CDCl_3$, 400 MHz)



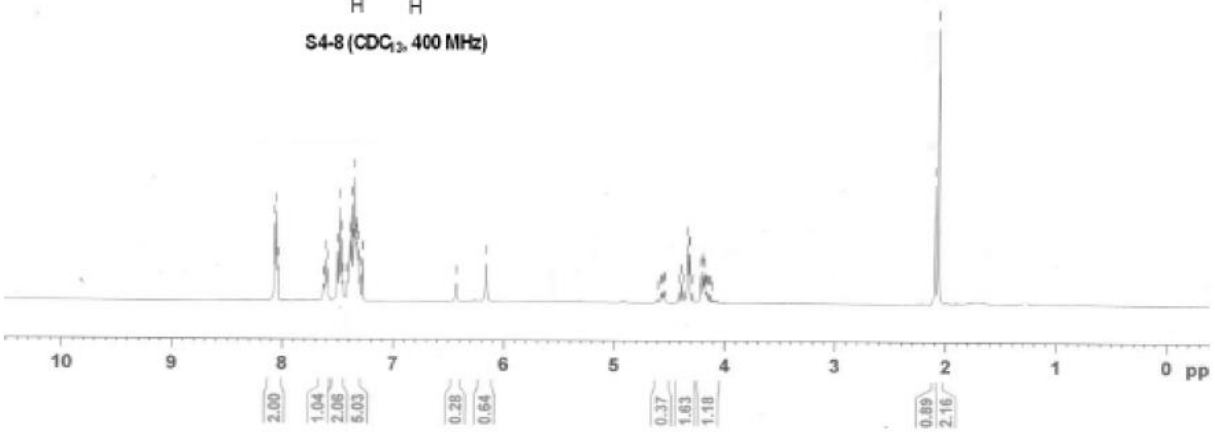
Ar = Ph-C≡C

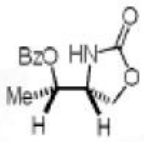
S4-7 ($CDCl_3$, 100 MHz)



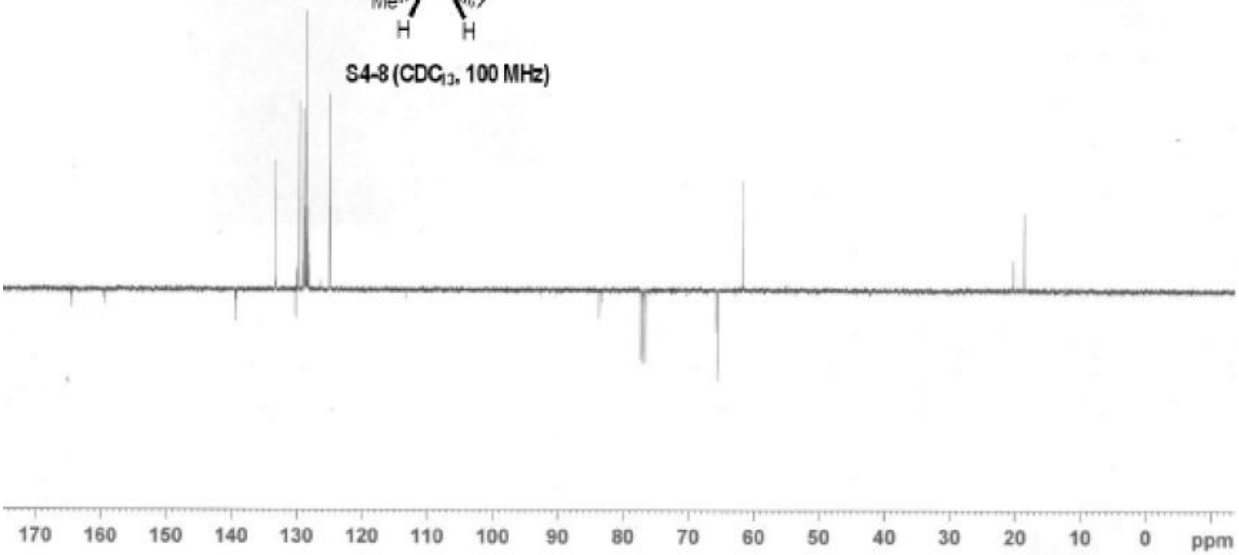


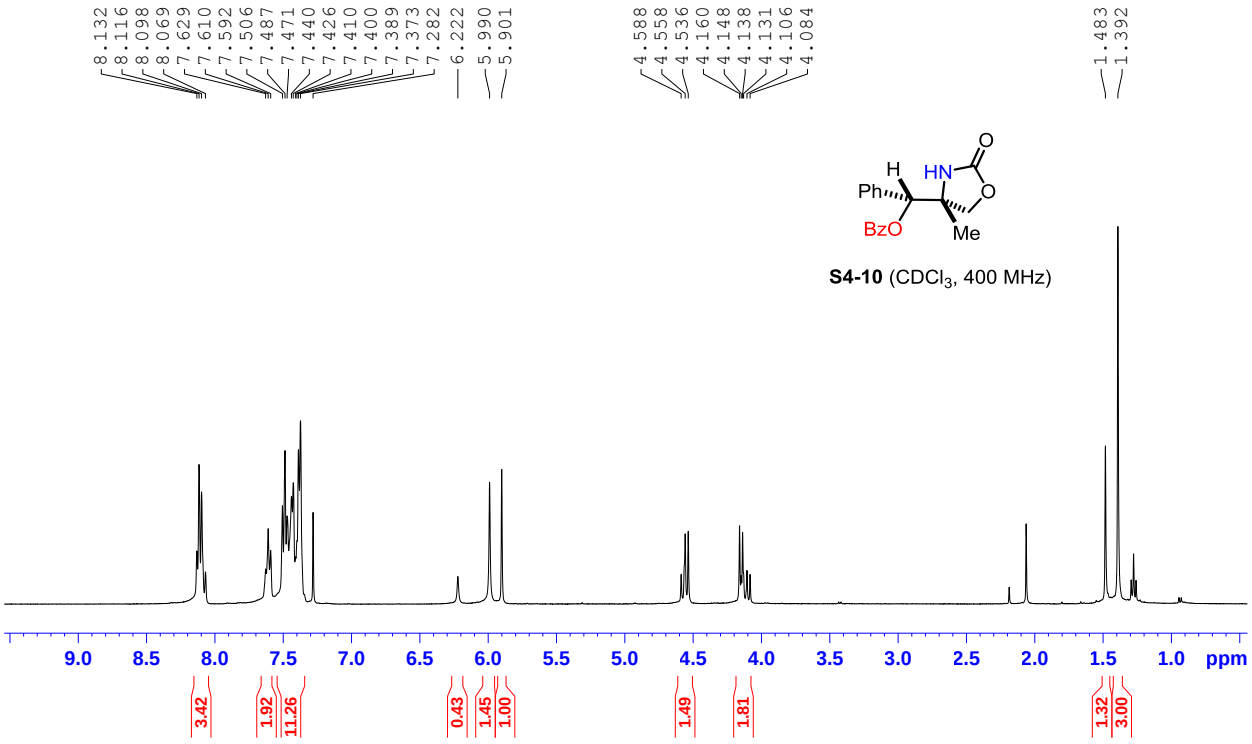
S4-8 (CDC_{13}, 400 MHz)



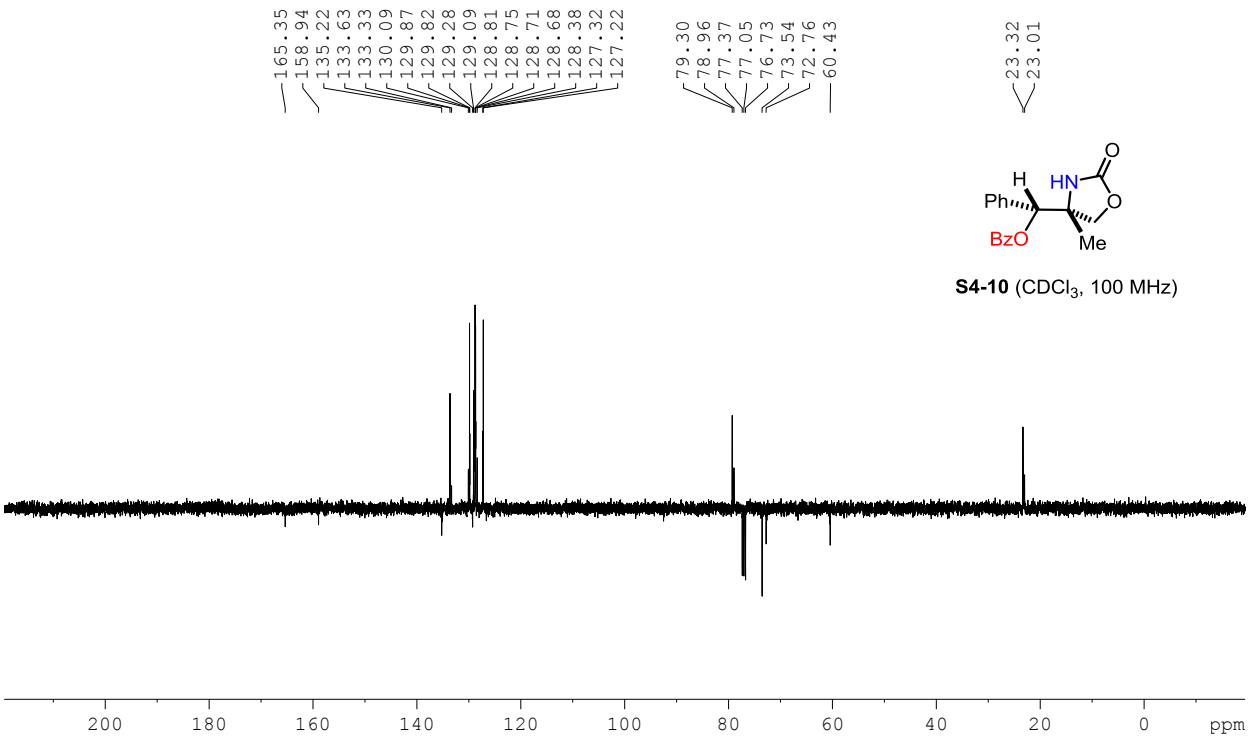


S4-8 (CDC_{13}, 100 MHz)

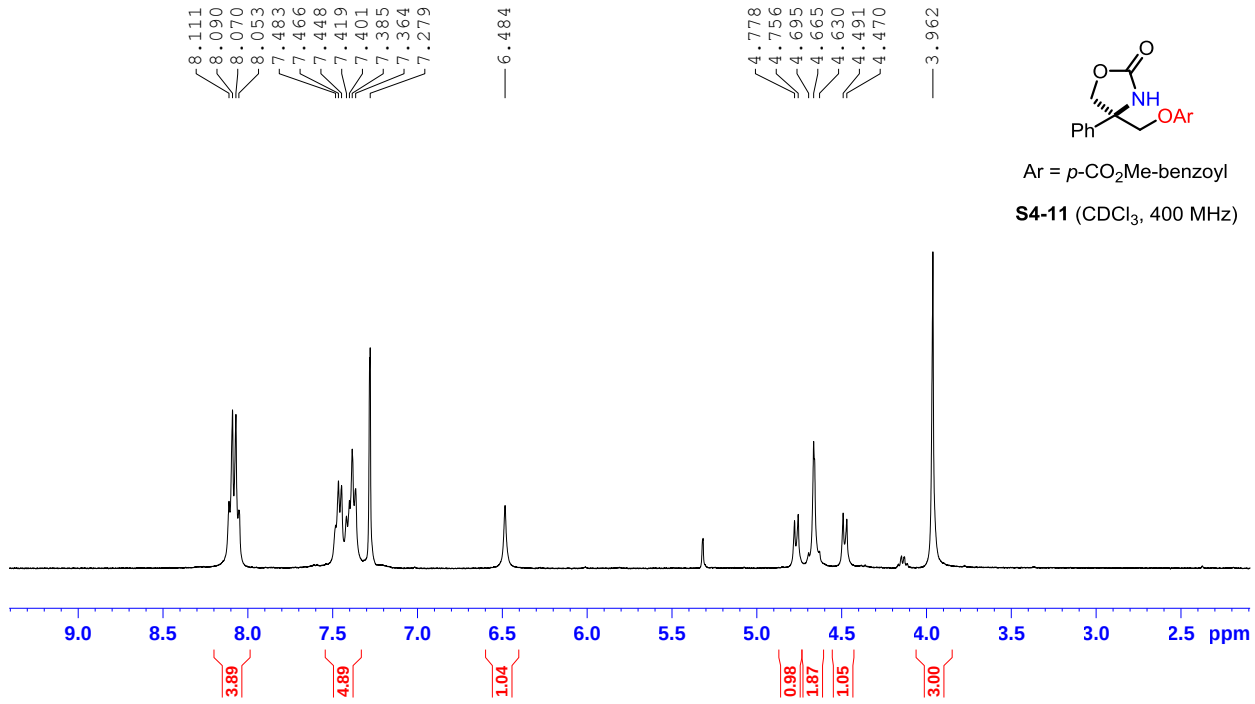




S4-10 ($CDCl_3$, 400 MHz)

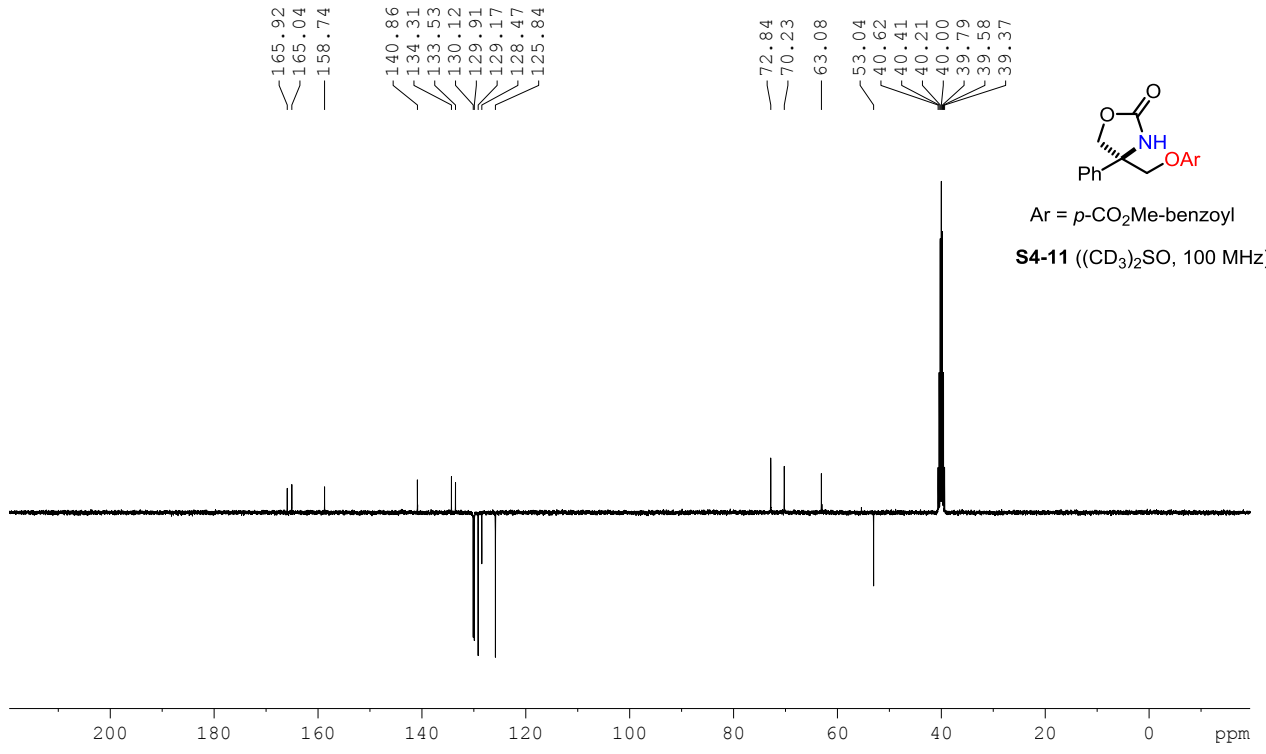


S4-10 ($CDCl_3$, 100 MHz)



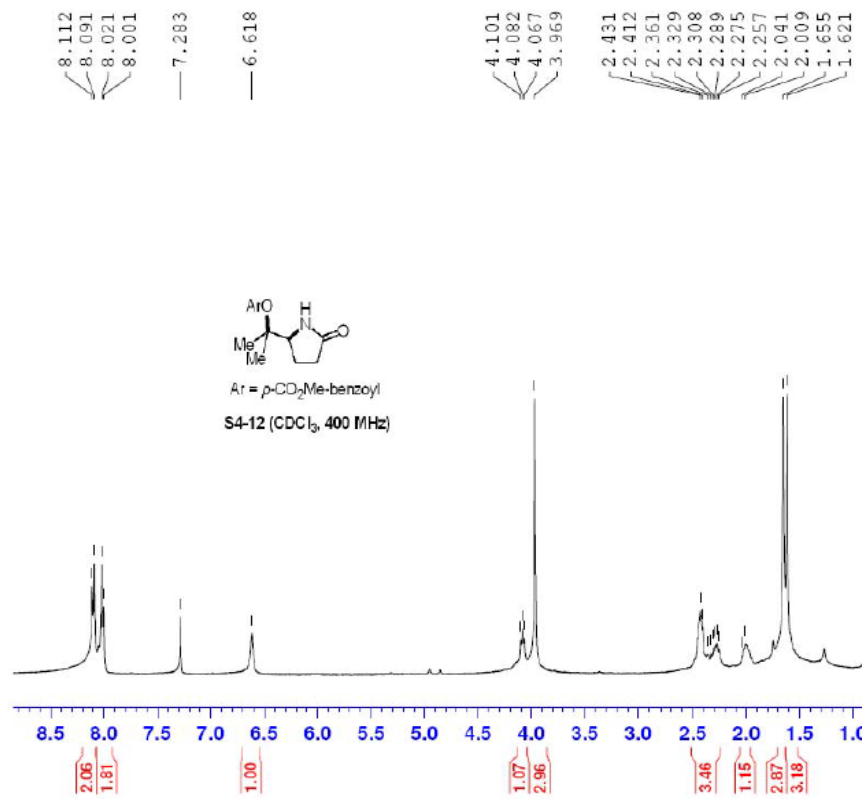
Ar = *p*-CO_2Me-benzoyl

S4-11 ($CDCl_3$, 400 MHz)

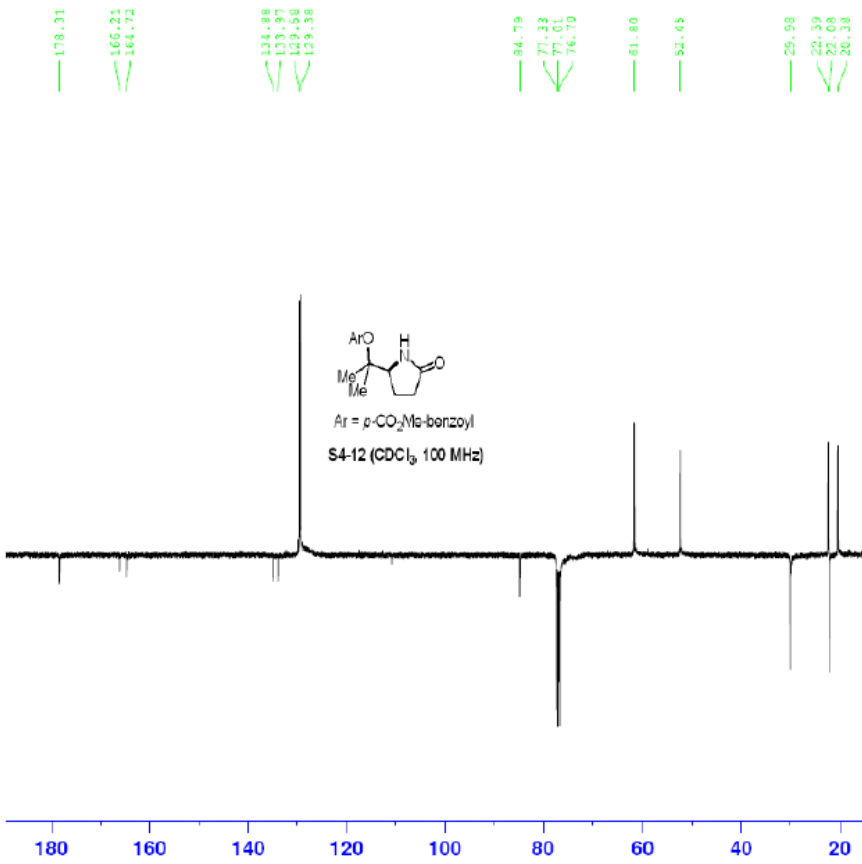


Ar = *p*-CO_2Me-benzoyl

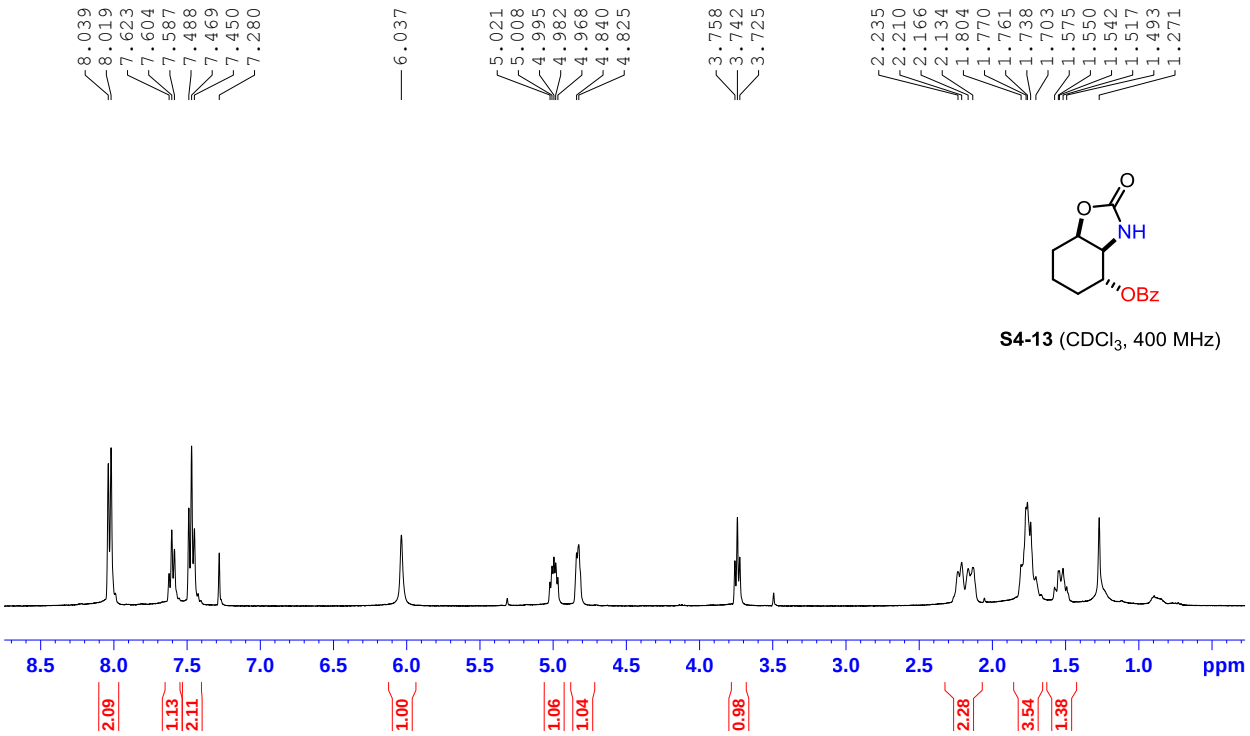
S4-11 ($(CD_3)_2SO$, 100 MHz)



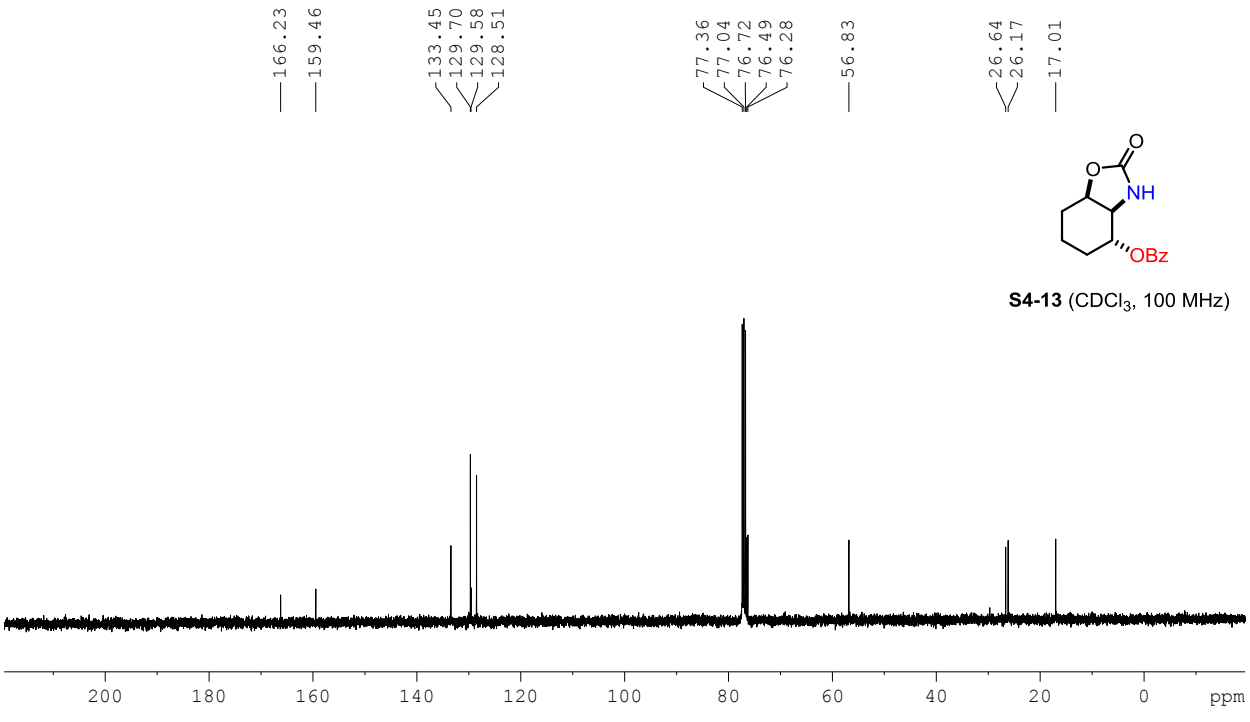

```
Current Data Parameters
NAME      GSL-IX-43 CuCN 3rd
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20120813
Time                 21.12
INSTRUM              spect
PROBHD    5 mm PABBO BB-
PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     10
DS                      2
SWH              8012.820 Hz
FIDRES           0.122266 Hz
AQ               4.0894465 sec
RG                    161
DW                 62.400 usec
DE                  6.50 usec
TE                300.0 K
D1             1.00000000 sec
TD0                     1

======== CHANNEL f1 ========
SFO1         400.1424710 MHz
NUC1                   1H
P1                  13.50 usec
PLW1         16.00000000 W

F2 - Processing parameters
SI                  65536
SF           400.1400000 MHz
WDW                    EM
SSB       0
LB                   0.30 Hz
GB        0
PC                   1.00
```



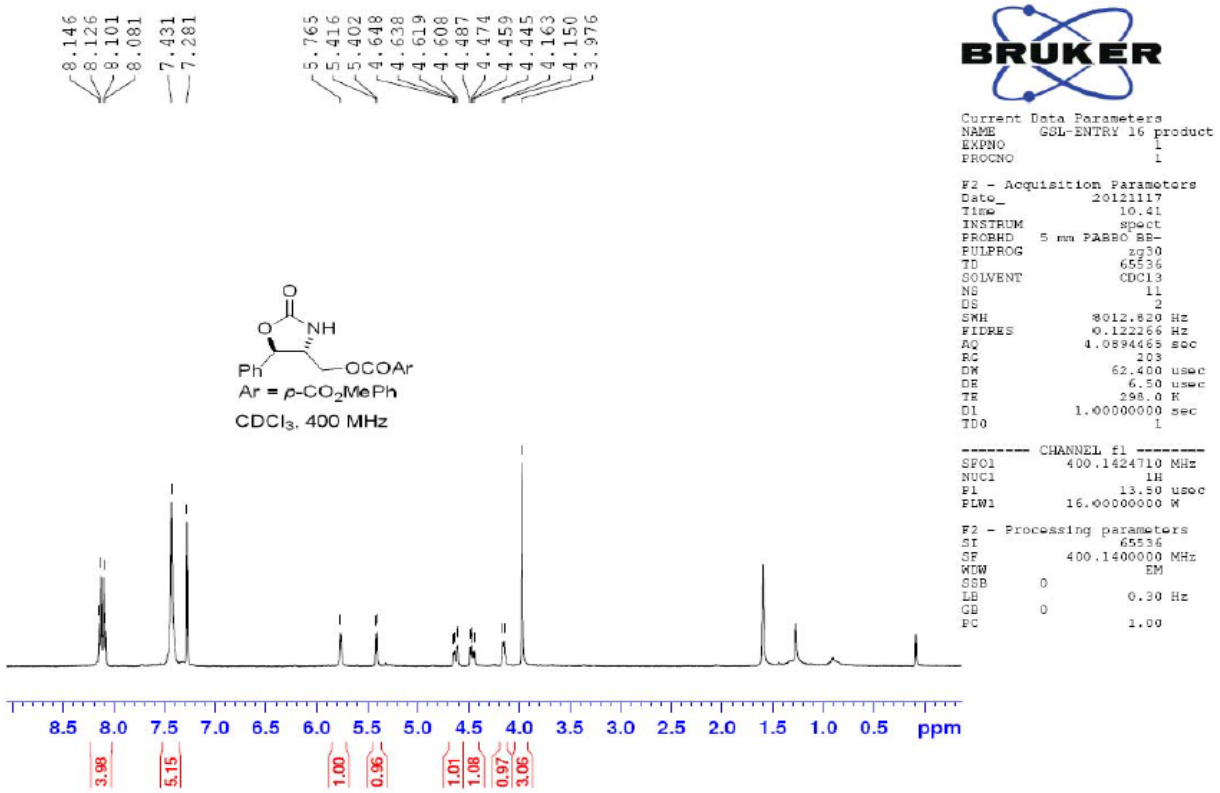

```
Current Data Parameters
NAME      GSL-IX-43 CuCN 3rd
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_              20120813
Time                 21.15
INSTRUM              spect
PROBHD    5 mm PABBO BB-
PULPROG             jmod
TD                  65536
SOLVENT             CDCl3
NS                  10000
DS                      4
SWH             24038.461 Hz
FIDRES           0.366798 Hz
AQ               1.3631488 sec
RG                    203
DW                 20.800 usec
DE                  6.50 usec
TE                300.7 K
CNST2          145.0000000
CNST11           1.0000000
D1             2.00000000 sec
D20            0.00689655 sec
TD0                     1

======== CHANNEL f1 ========
SFO1         100.6253446 MHz
NUC1                   13C
P1                   9.00 usec
P2                  18.00 usec
PLW1         62.00000000 W

======== CHANNEL f2 ========
SFO2         400.1416006 MHz
NUC2                   1H
CPDPRG[2           waltz16
PCPD2               90.00 usec
PLW2         16.00000000 W
PLW12         0.36000001 W

F2 - Processing parameters
SI                  32768
SF           100.6152830 MHz
WDW                    EM
SSB       0
LB                   1.00 Hz
GB        0
PC                   1.40
```

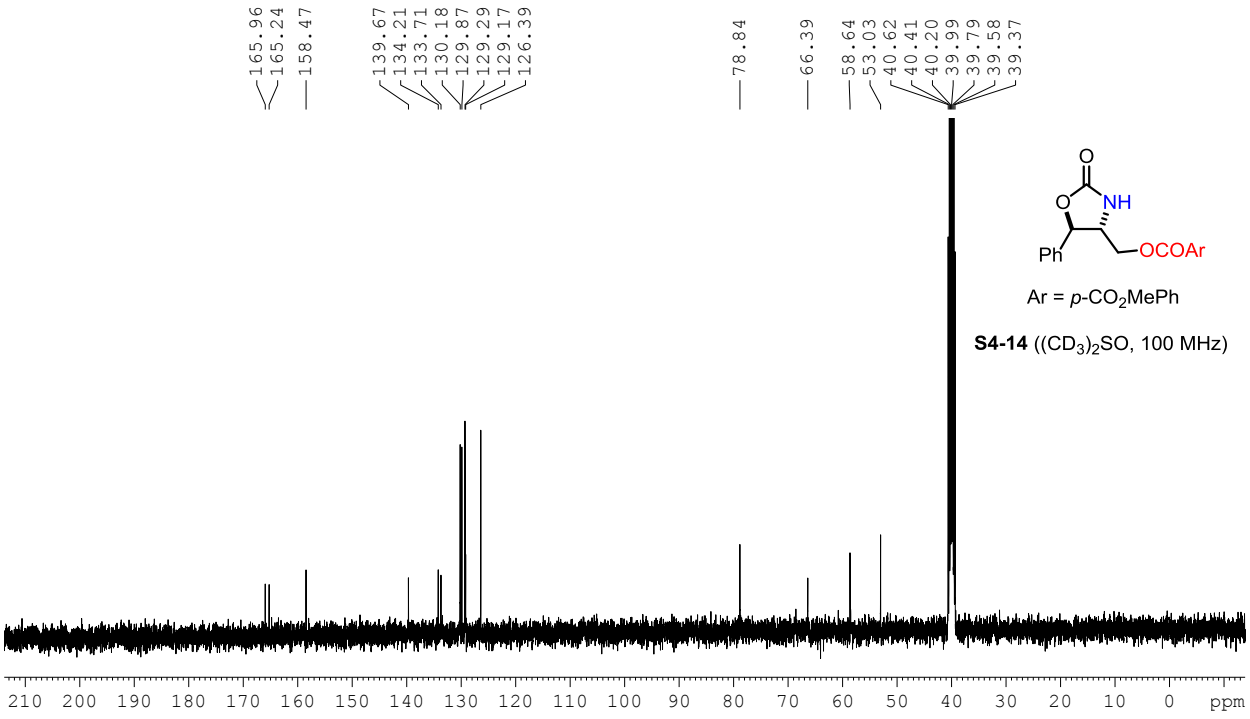


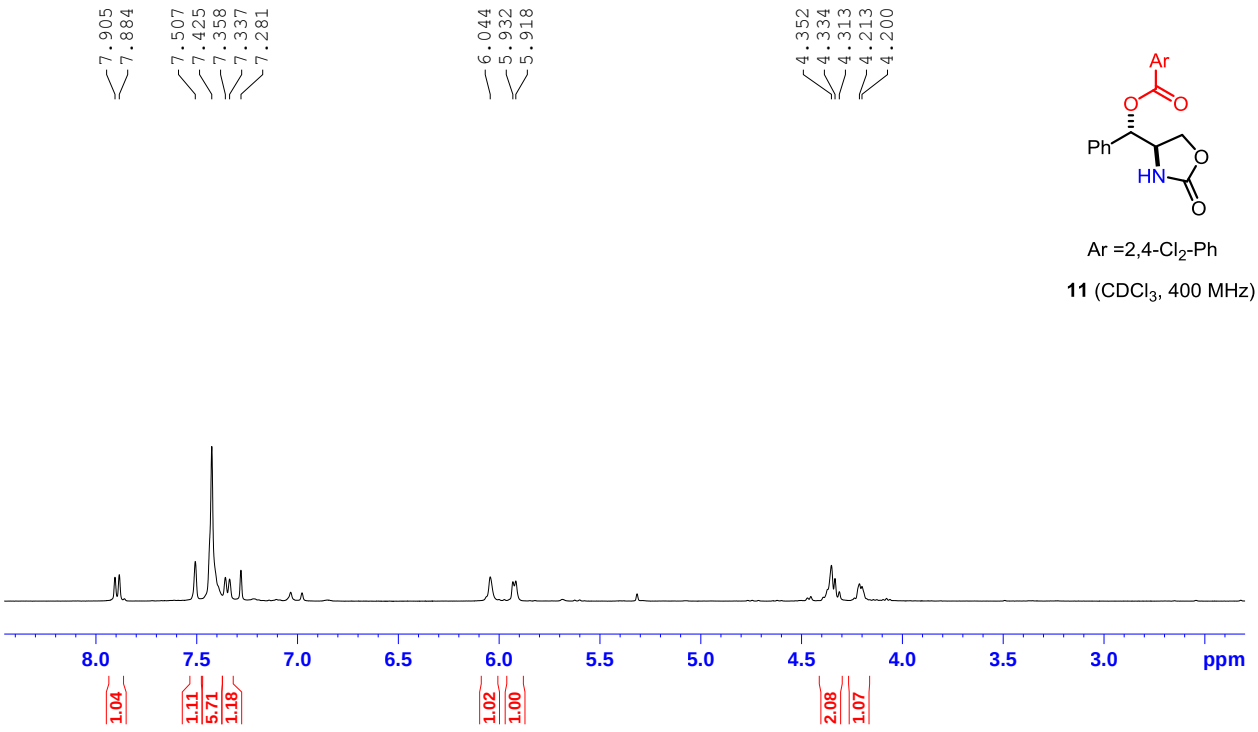
S4-13 ($CDCl_3$, 400 MHz)



S4-13 ($CDCl_3$, 100 MHz)

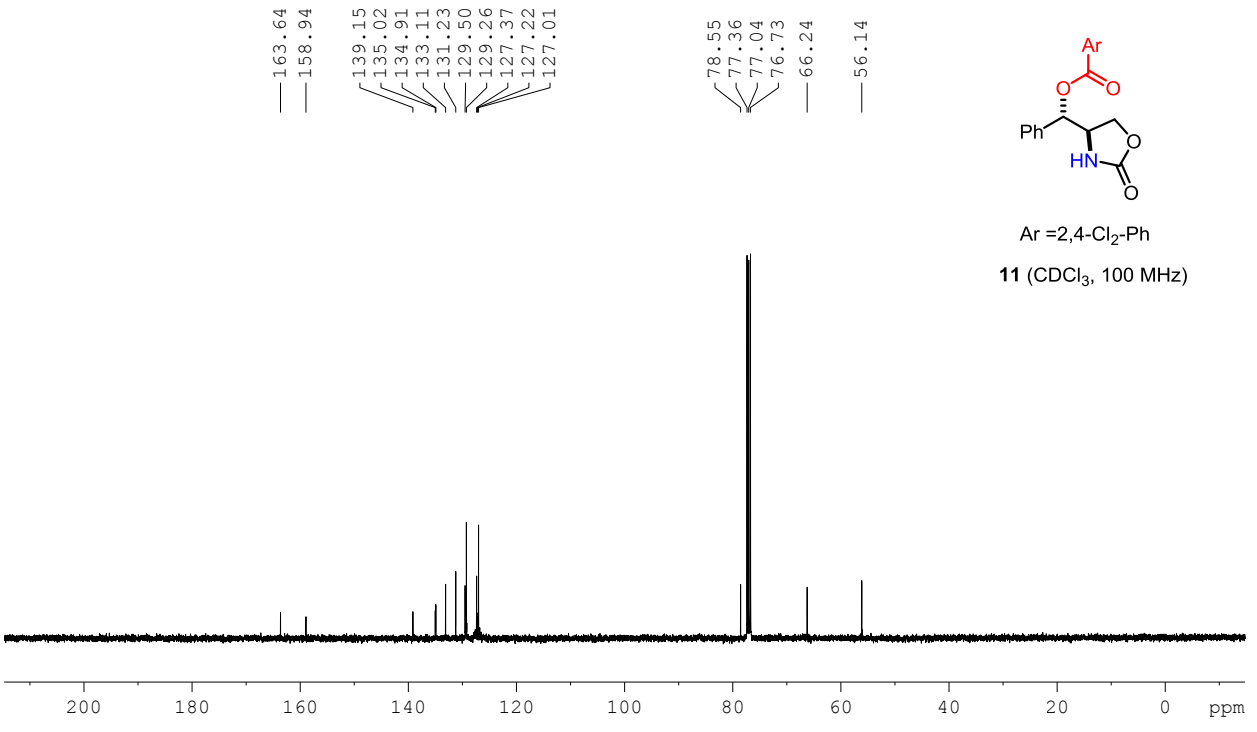

8.146
8.126
8.101
8.081
7.431
7.281
5.765
5.416
5.402
4.648
4.638
4.619
4.608
4.487
4.474
4.459
4.445
4.163
4.150
3.976
BRUKER
Current Data Parameters
NAME GSL-ENTRY 16 product
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121117
Time 16.41
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 11
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894465 sec
RG 203
DW 62.400 usec
DE 6.50 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
SFO1 400.1424710 MHz
NUC1 1H
PL 13.50 usec
PLW1 16.00000000 W
F2 - Processing parameters
SI 65536
SF 400.1400000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
O
NH
O
Ph
OCOAr
Ar = p-CO2MePh
CDCl3, 400 MHz
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
3.98
5.15
1.00
0.96
1.01
1.08
0.97
3.06


165.96
165.24
158.47
139.67
134.21
133.71
130.18
129.87
129.29
129.17
126.39
78.84
66.39
58.64
53.03
40.62
40.41
40.20
39.99
39.79
39.58
39.37
O
NH
O
Ph
OCOAr
Ar = p-CO2MePh
S4-14 ((CD3)2SO, 100 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



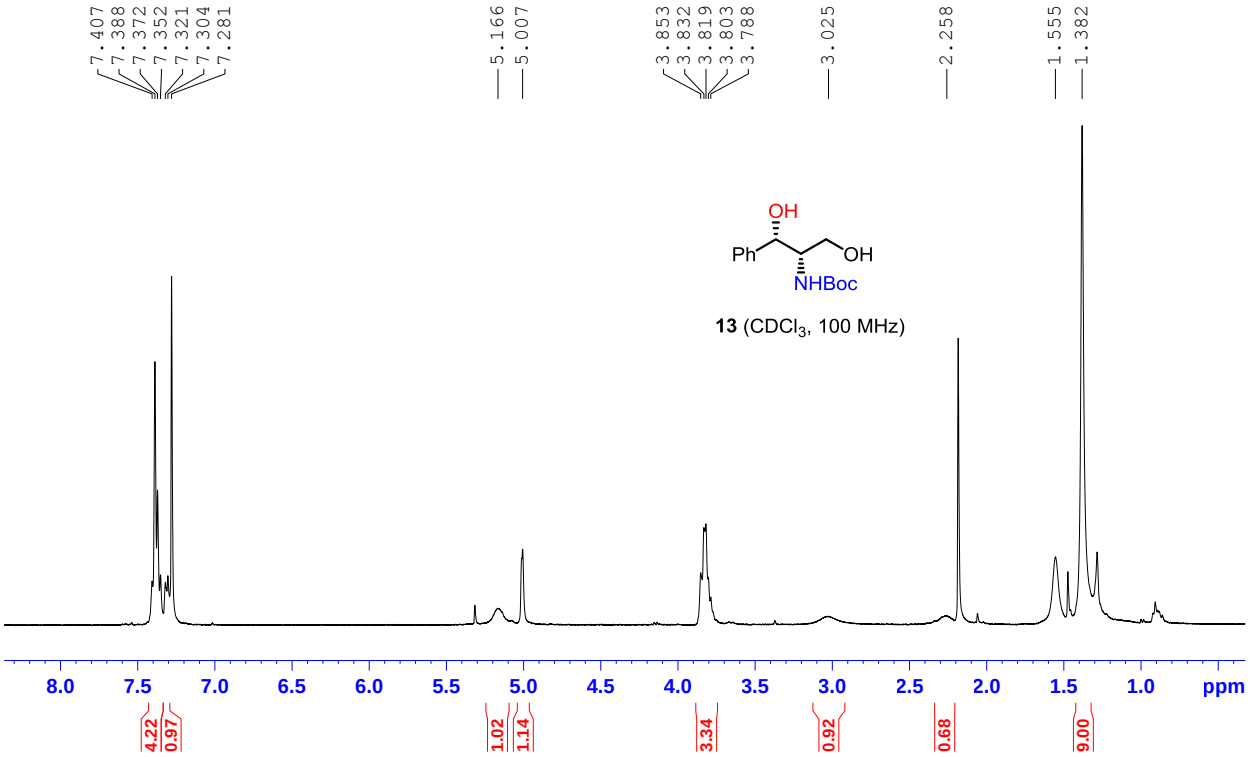
Ar =2,4-Cl_2-Ph

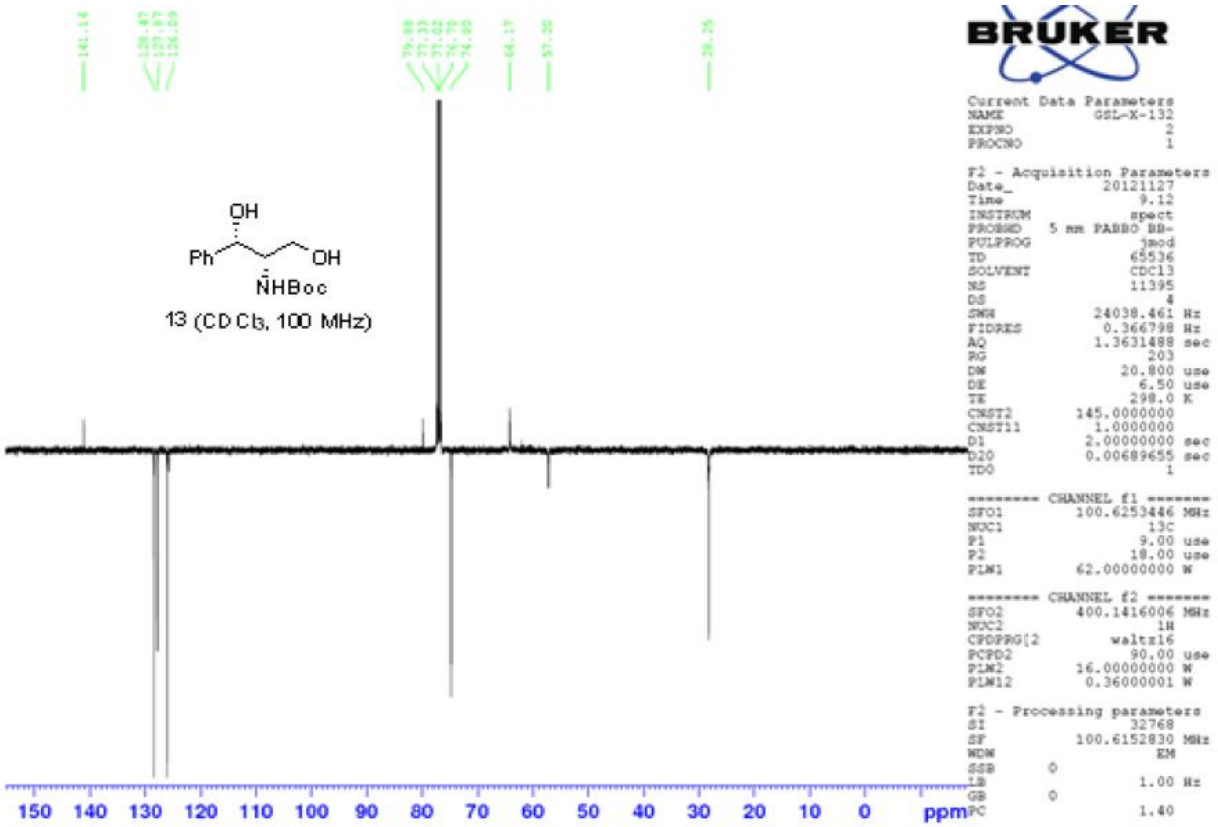
11 ($CDCl_3$, 400 MHz)



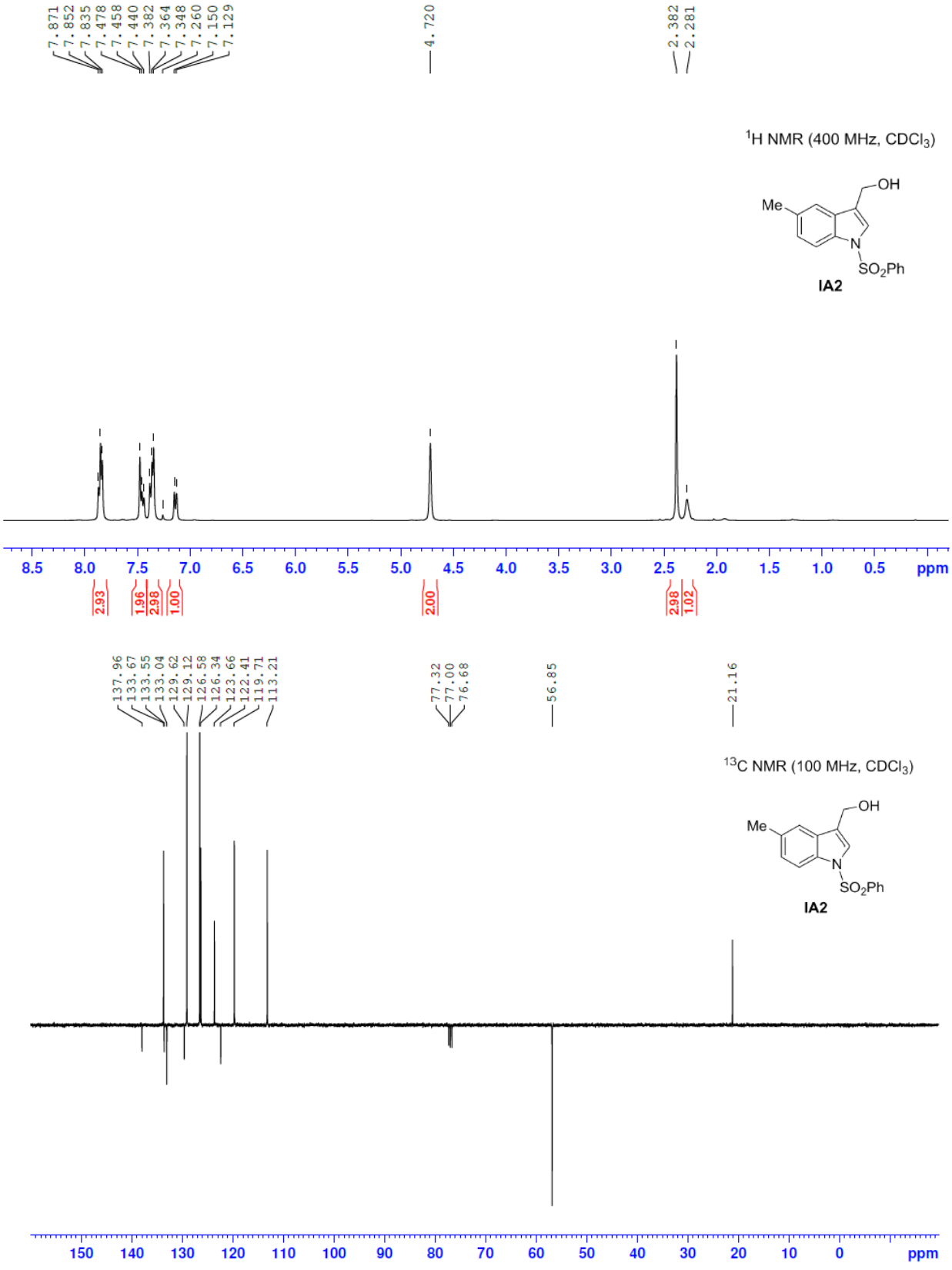
Ar =2,4-Cl_2-Ph

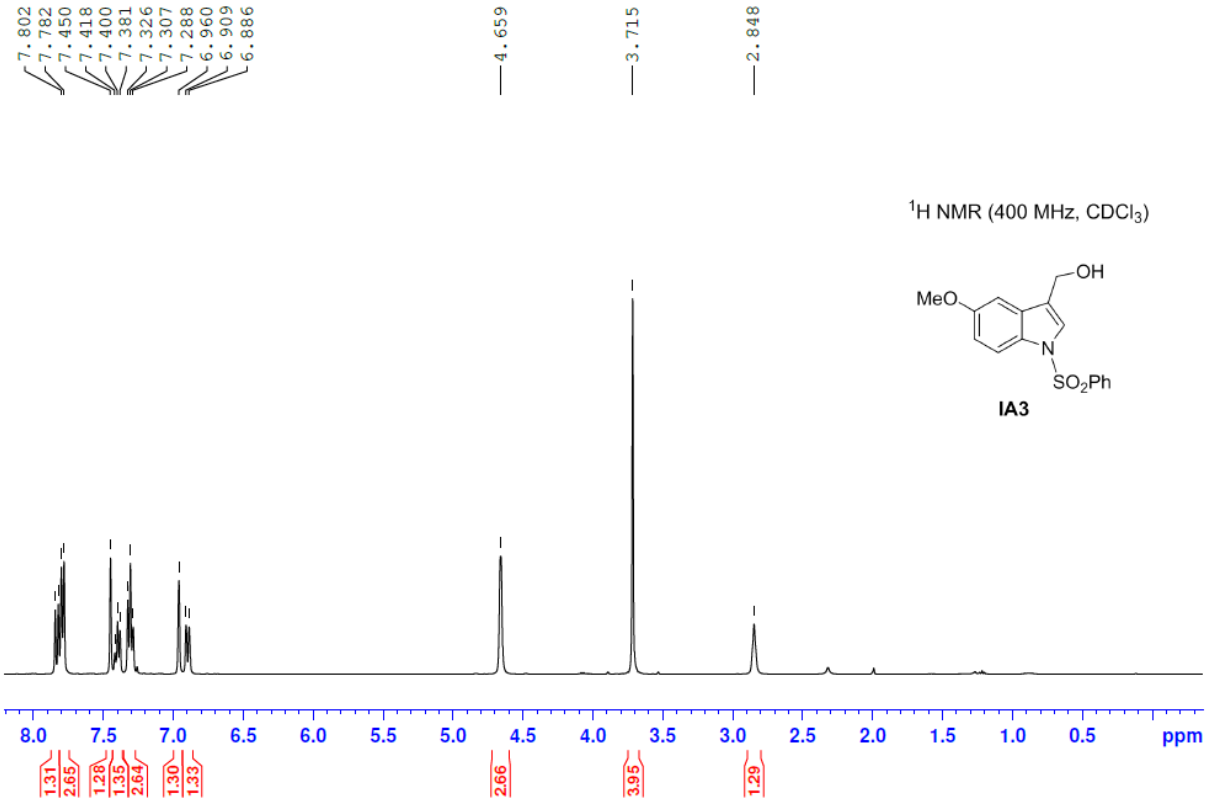
11 ($CDCl_3$, 100 MHz)

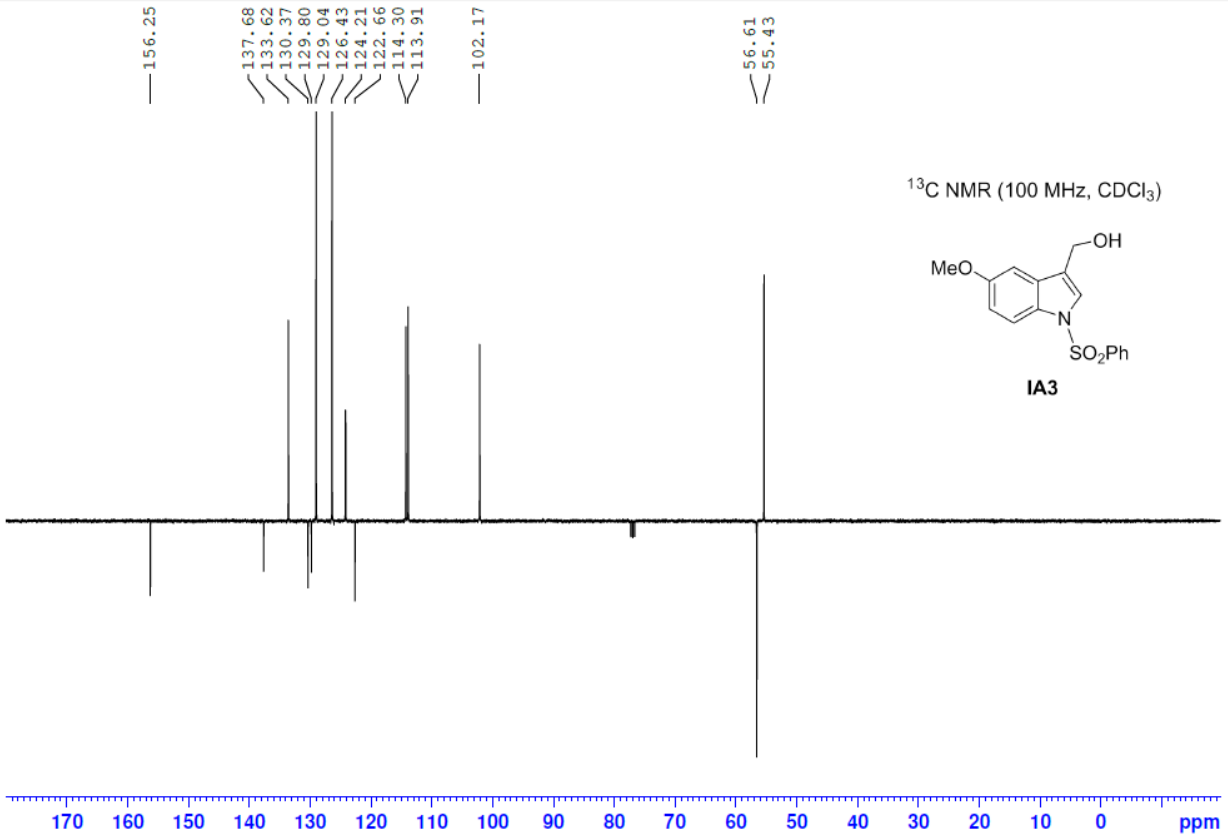

7.407
7.388
7.372
7.352
7.321
7.304
7.281
5.166
5.007
3.853
3.832
3.819
3.803
3.788
3.025
2.258
1.555
1.382
OH
Ph
OH
NHBoc
13 (CDCl3, 100 MHz)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
4.22
0.97
1.02
1.14
3.34
0.92
0.68
9.00

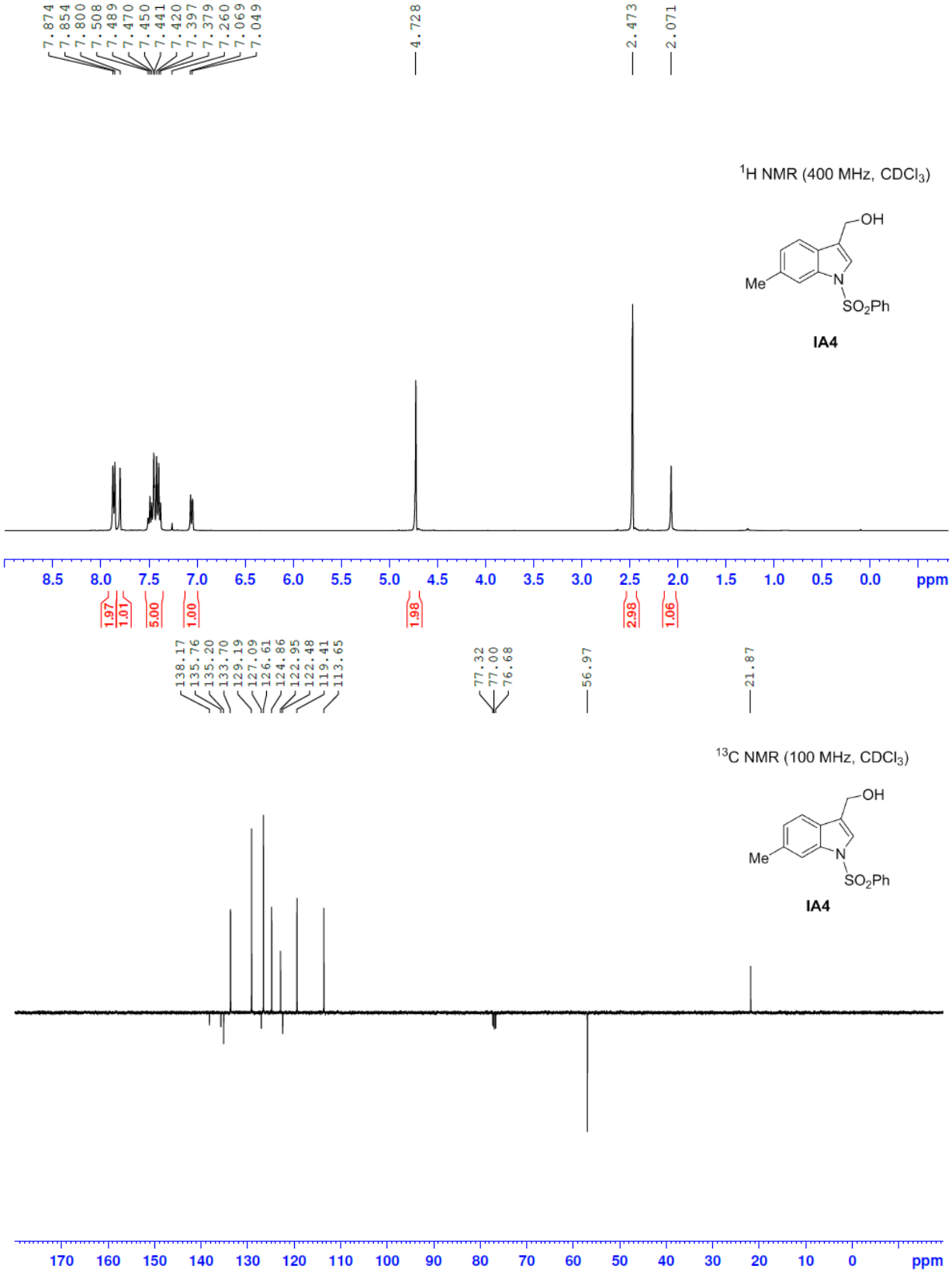

OH
Ph
OH
NHBoc
13 (CDCl3, 100 MHz)
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm
BRUKER
Current Data Parameters
NAME GSL-X-132
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121127
Time 9.12
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 11395
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 203
DW 20.800 usec
DE 6.50 usec
TE 298.0 K
CNST2 145.0000000
CNST11 1.0000000
D1 2.00000000 sec
D20 0.00689655 sec
TD0 1
======== CHANNEL f1 ========
SFO1 100.6253446 MHz
NUC1 13C
P1 9.00 usec
P2 18.00 usec
PLW1 62.00000000 W
======== CHANNEL f2 ========
SFO2 400.1416006 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 16.00000000 W
PLW12 0.36000001 W
F2 - Processing parameters
SI 32768
SF 100.6152830 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

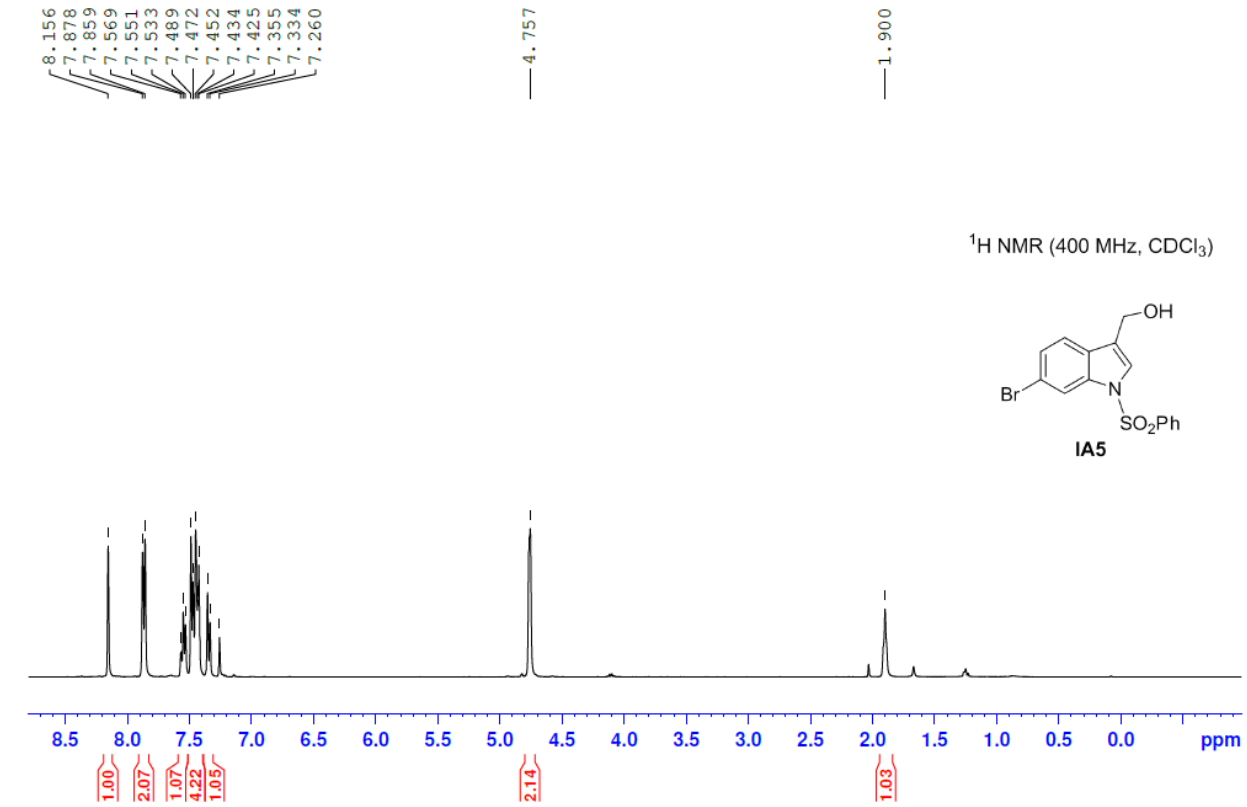
Appendix C ^{1}H and ^{13}C Spectra of Compounds in Chapter III

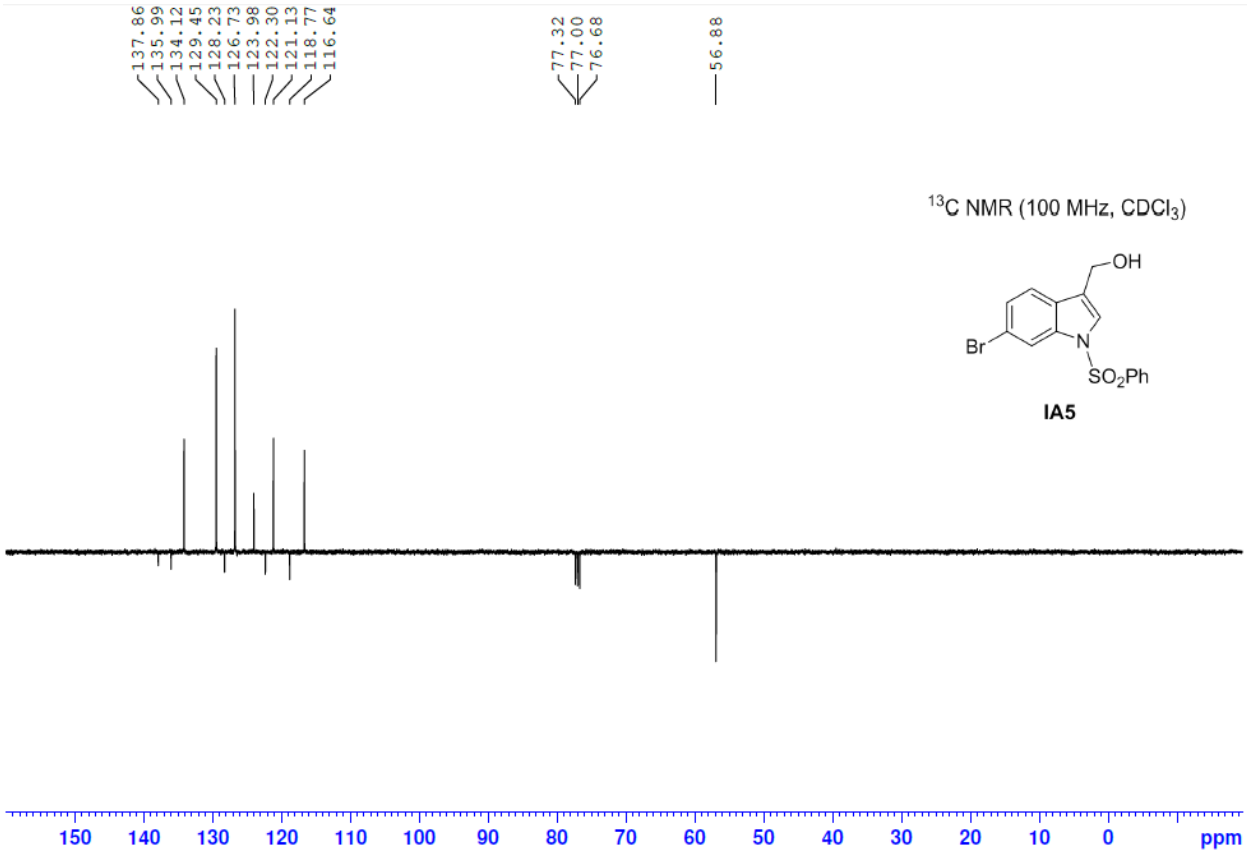


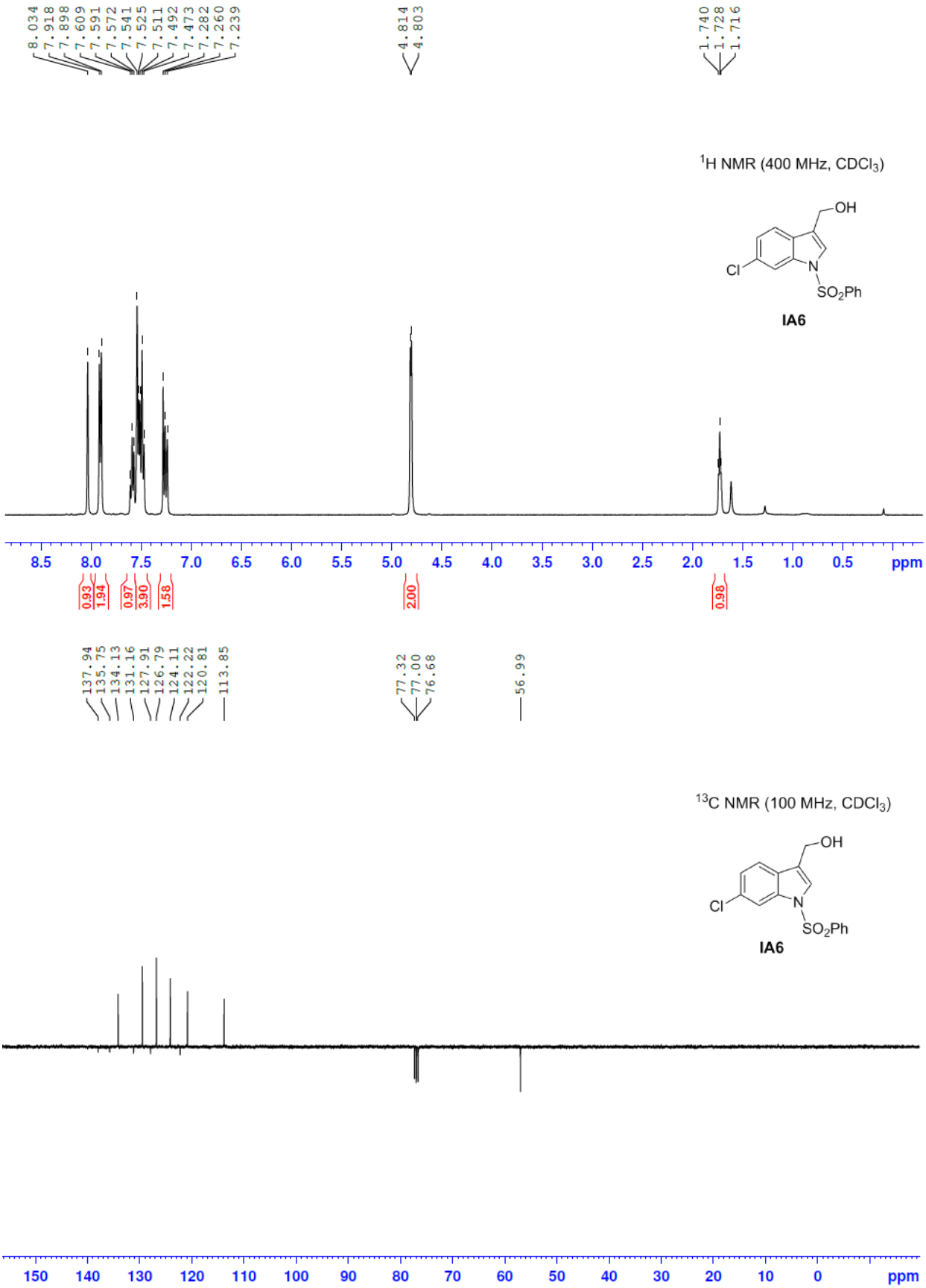

7.802
7.782
7.450
7.418
7.400
7.381
7.326
7.307
7.288
6.960
6.909
6.886
4.659
3.715
2.848
1H NMR (400 MHz, CDCl3)
OH
MeO
N
SO2Ph
IA3
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.31
2.65
1.28
1.35
2.64
1.30
1.33
2.66
3.95
1.29

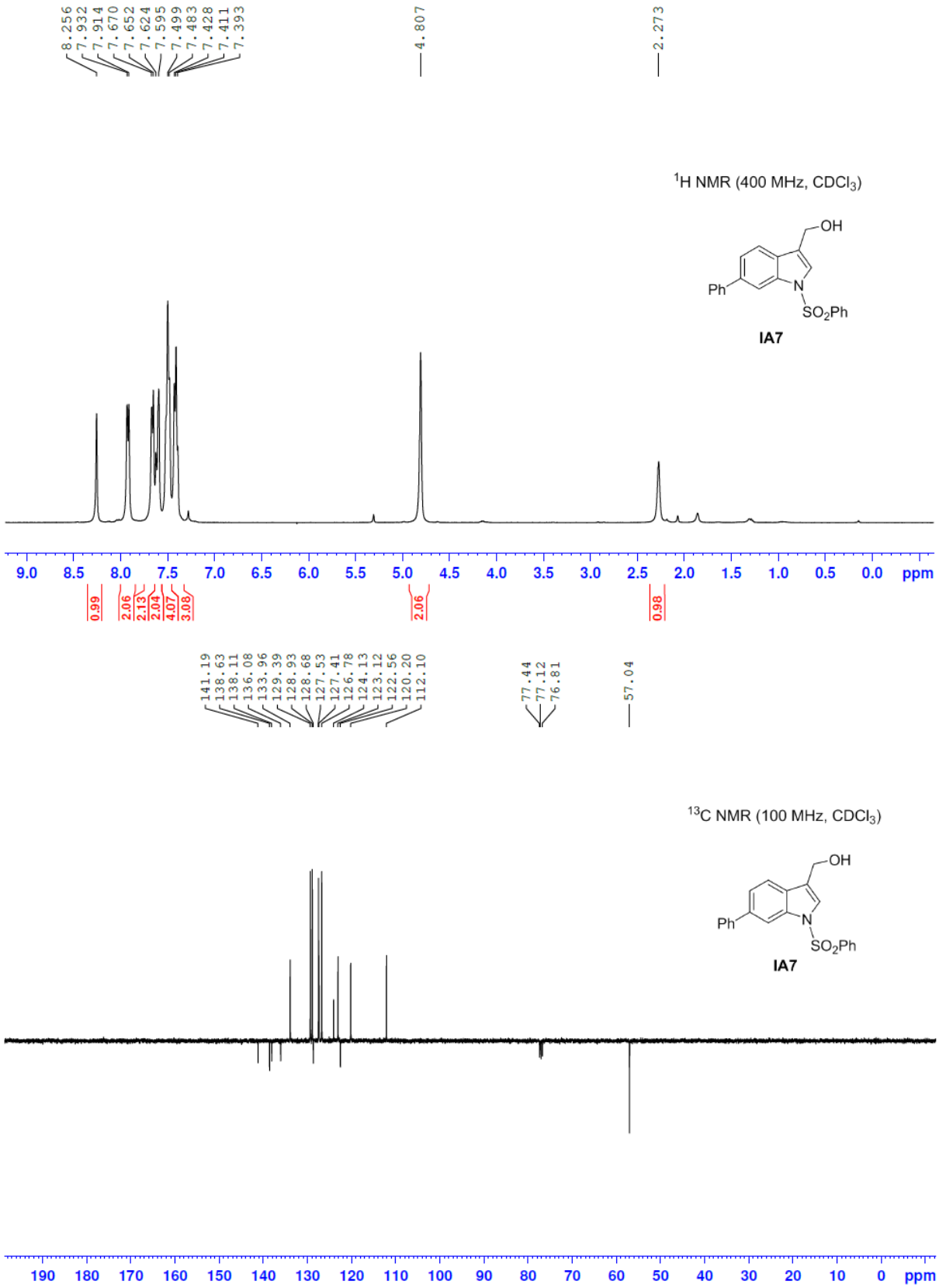

156.25
137.68
133.62
130.37
129.80
129.04
126.43
124.21
122.66
114.30
113.91
102.17
56.61
55.43
13C NMR (100 MHz, CDCl3)
OH
MeO
N
SO2Ph
IA3
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

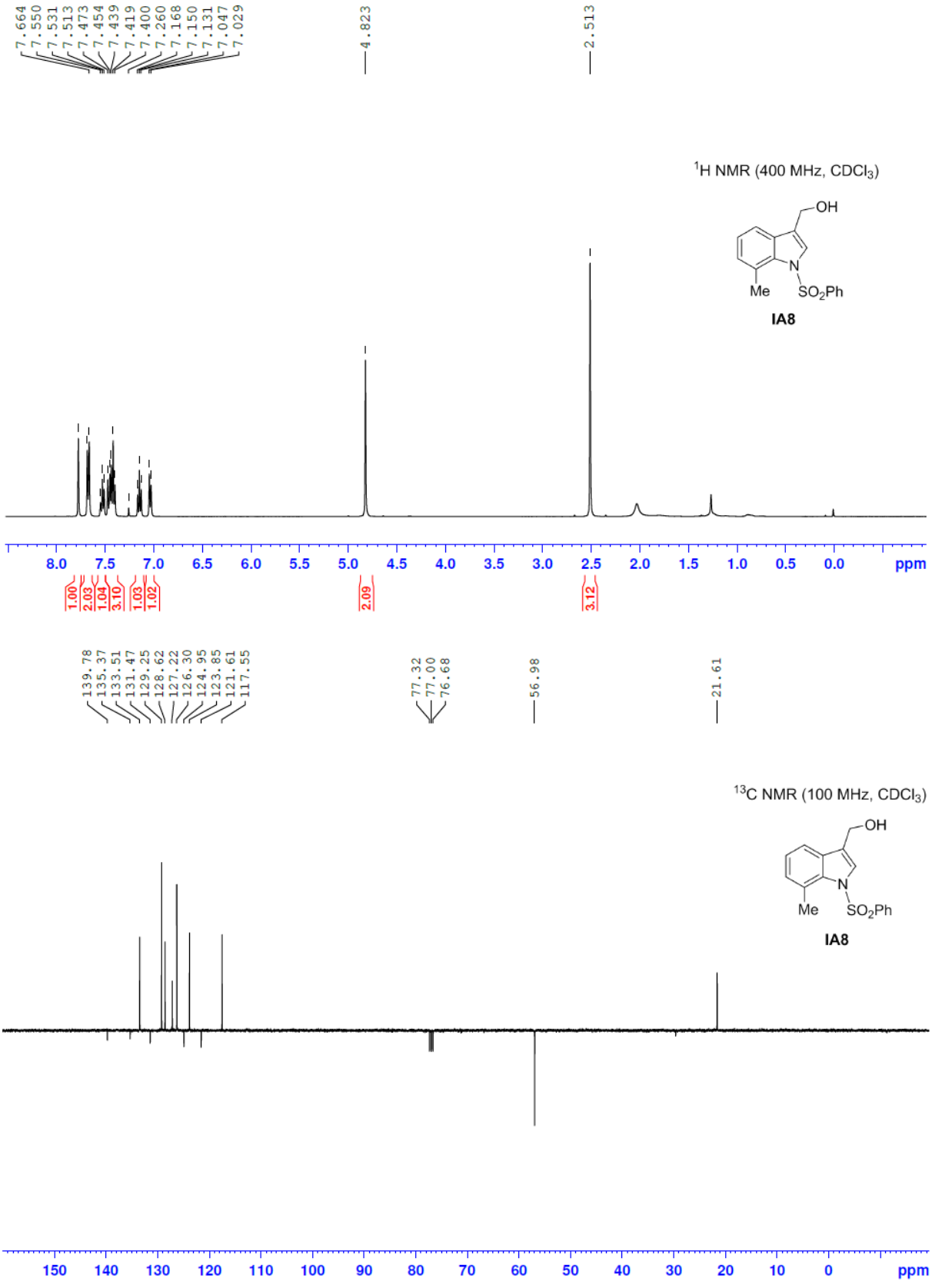

7.874
7.854
7.800
7.508
7.489
7.470
7.450
7.441
7.420
7.397
7.379
7.260
7.069
7.049
4.728
2.473
2.071
1H NMR (400 MHz, CDCl3)
OH
Me
N
SO2Ph
IA4
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.97
1.01
5.00
1.00
1.98
2.98
1.06
138.17
135.76
135.20
133.70
129.19
127.09
126.61
124.86
122.95
122.48
119.41
113.65
77.32
77.00
76.68
56.97
21.87
13C NMR (100 MHz, CDCl3)
OH
Me
N
SO2Ph
IA4
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

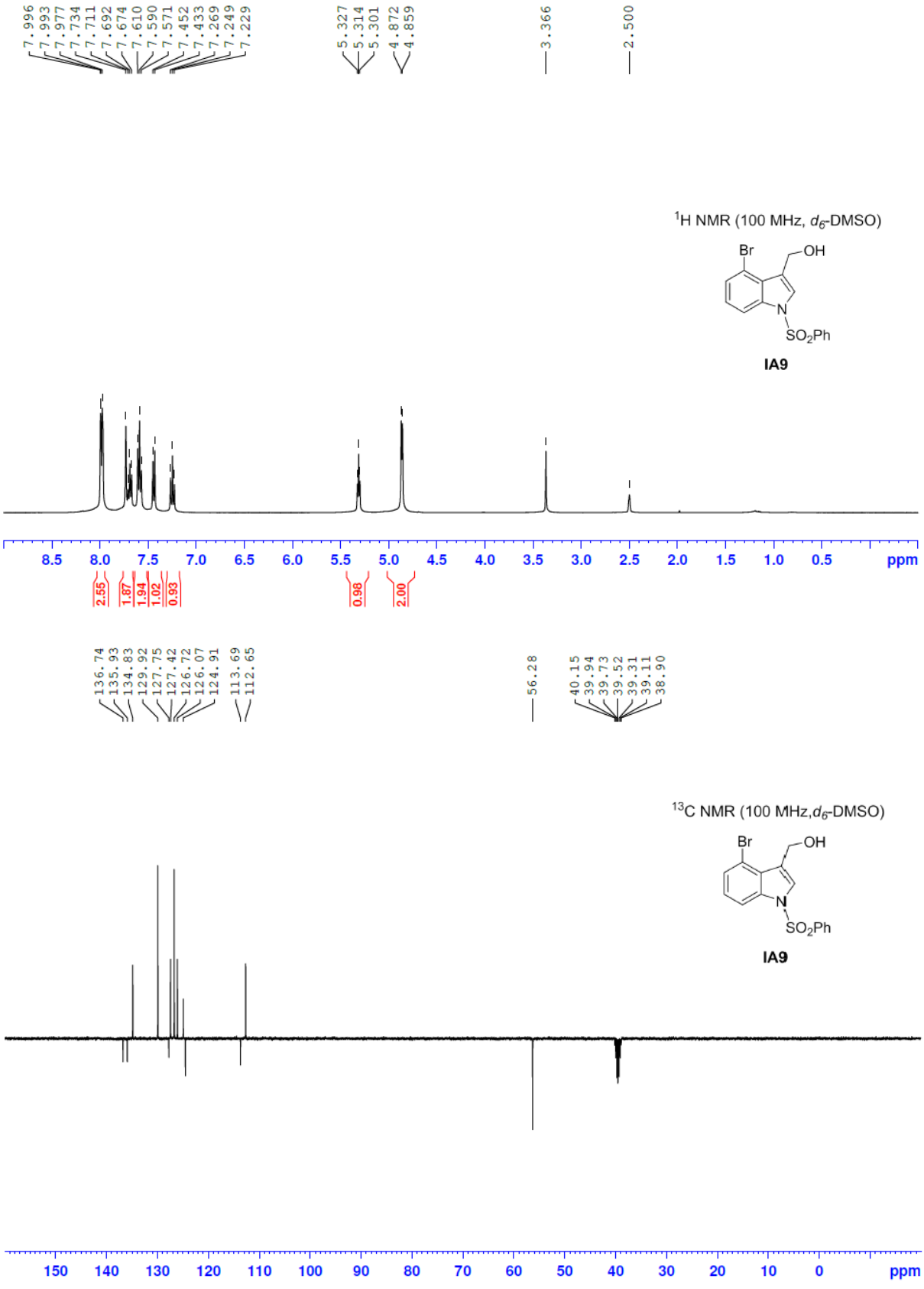

8.156
7.878
7.859
7.569
7.551
7.533
7.489
7.472
7.452
7.434
7.425
7.355
7.334
7.260
4.757
1.900
1H NMR (400 MHz, CDCl3)
OH
Br
N
SO2Ph
IA5
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.00
2.07
1.07
4.22
1.05
2.14
1.03

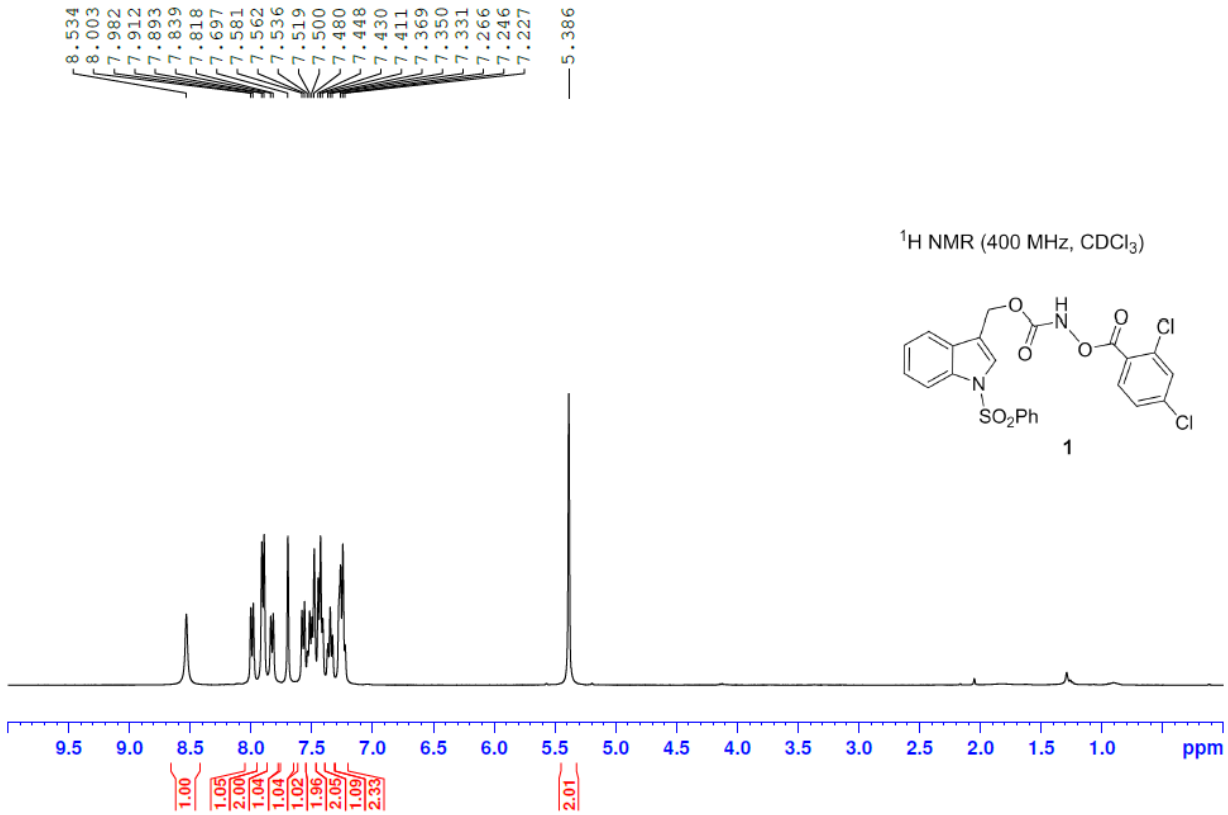

137.86
135.99
134.12
129.45
128.23
126.73
123.98
122.30
121.13
118.77
116.64
77.32
77.00
76.68
56.88
13C NMR (100 MHz, CDCl3)
OH
Br
N
SO2Ph
IA5
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

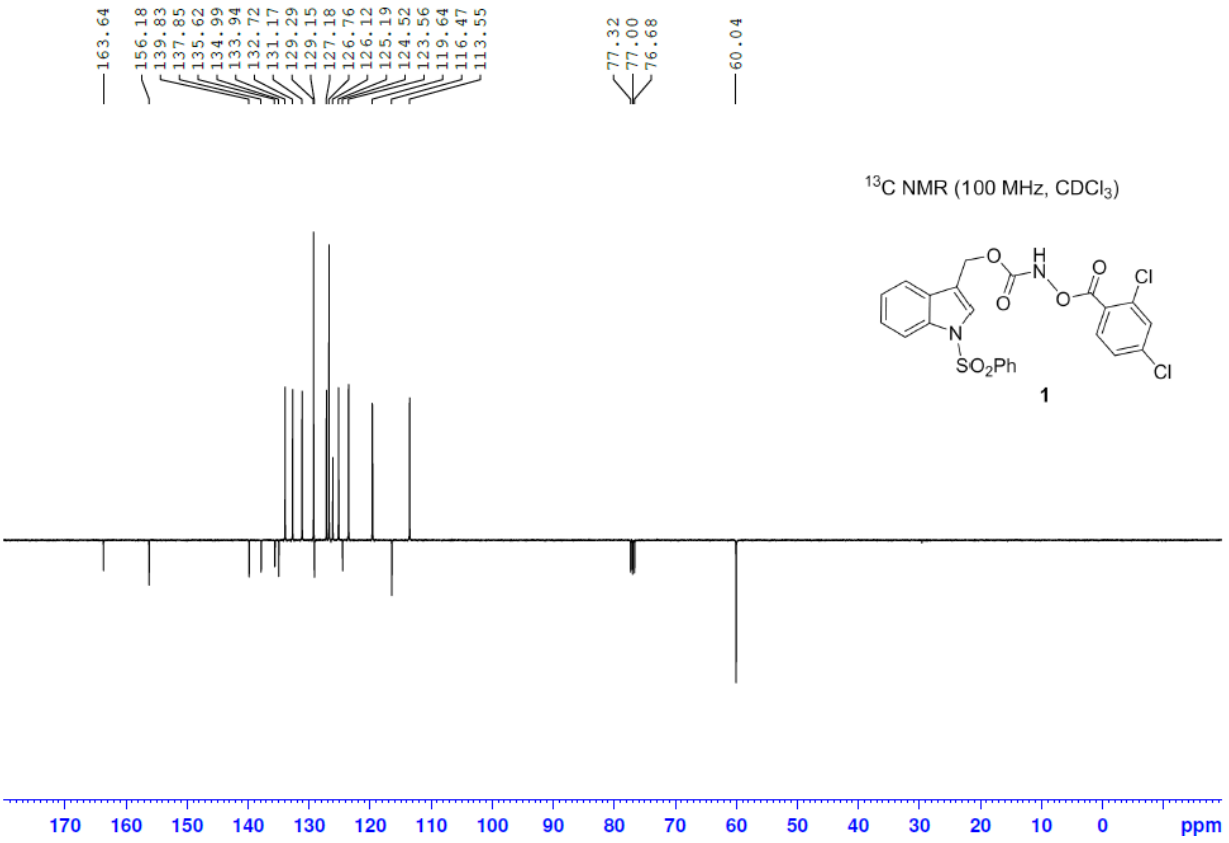

8.034
7.918
7.898
7.609
7.591
7.572
7.541
7.525
7.511
7.492
7.473
7.282
7.260
7.239
4.814
4.803
1.740
1.728
1.716
1H NMR (400 MHz, CDCl3)
OH
Cl
N
SO2Ph
IA6
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.93
1.94
0.97
3.90
1.58
2.00
0.98
137.94
135.75
134.13
131.16
127.91
126.79
124.11
122.22
120.81
113.85
77.32
77.00
76.68
56.99
13C NMR (100 MHz, CDCl3)
OH
Cl
N
SO2Ph
IA6
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

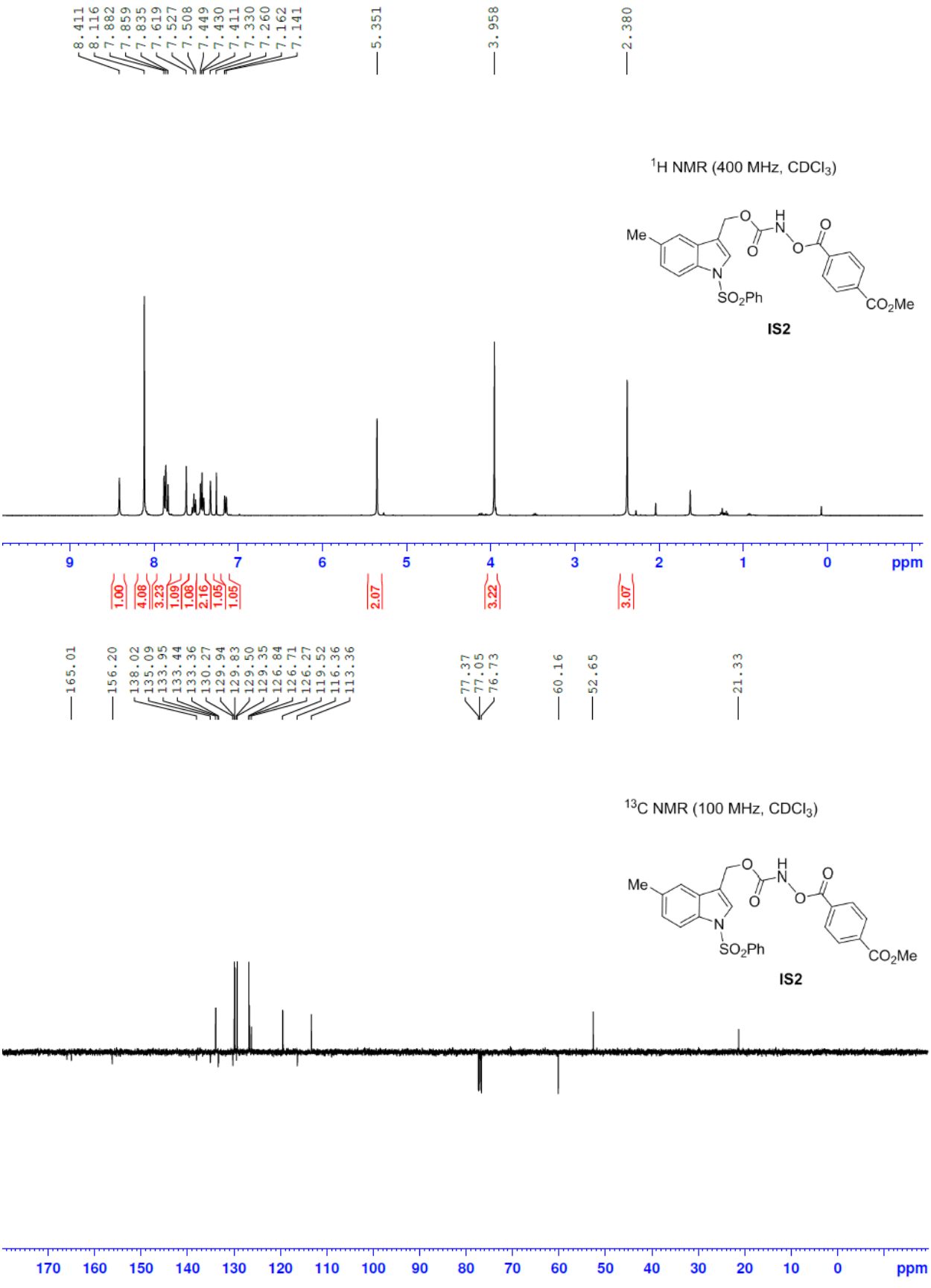

8.256
7.932
7.914
7.670
7.652
7.624
7.595
7.499
7.483
7.428
7.411
7.393
4.807
2.273
^{1}H NMR (400 MHz, CDCl$_3$)
OH
Ph
N
SO$_2$Ph
IA7
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
0.99
2.06
2.13
2.04
4.07
3.08
2.06
0.98
141.19
138.63
138.11
136.08
133.96
129.39
128.93
128.68
127.53
127.41
126.78
124.13
123.12
122.56
120.20
112.10
77.44
77.12
76.81
57.04
^{13}C NMR (100 MHz, CDCl$_3$)
OH
Ph
N
SO$_2$Ph
IA7
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

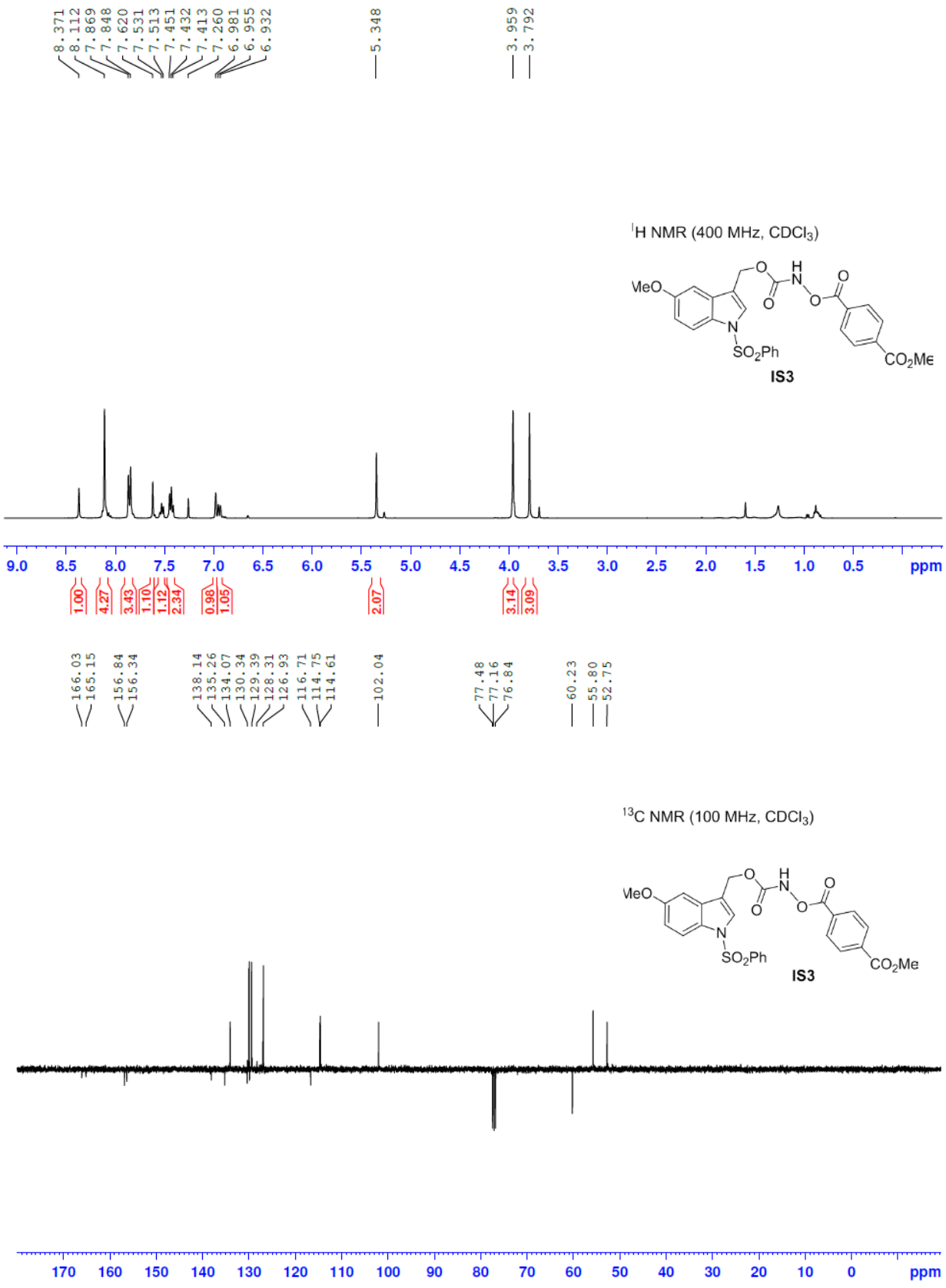

7.664
7.550
7.531
7.513
7.473
7.454
7.439
7.419
7.400
7.260
7.168
7.150
7.131
7.047
7.029
4.823
2.513
1H NMR (400 MHz, CDCl3)
OH
N
Me
SO2Ph
IA8
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.00
2.03
1.04
3.10
1.03
1.02
2.09
3.12
139.78
135.37
133.51
131.47
129.25
128.62
127.22
126.30
124.95
123.85
121.61
117.55
77.32
77.00
76.68
56.98
21.61
13C NMR (100 MHz, CDCl3)
OH
N
Me
SO2Ph
IA8
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

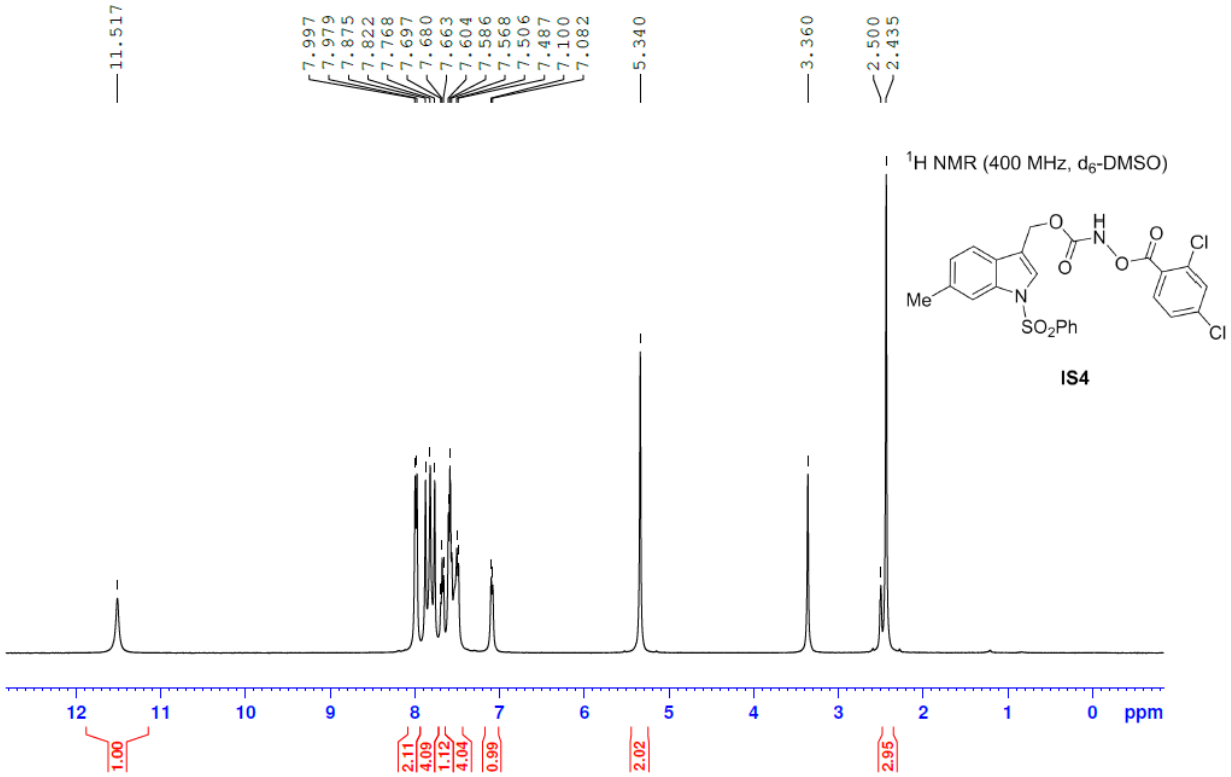

7.996
7.993
7.977
7.734
7.711
7.692
7.674
7.610
7.590
7.571
7.452
7.433
7.269
7.249
7.229
5.327
5.314
5.301
4.872
4.859
3.366
2.500
^{1}H NMR (100 MHz, d_6-DMSO)
Br
OH
N
SO_2Ph
IA9
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.55
1.87
1.94
1.02
0.93
0.98
2.00
136.74
135.93
134.83
129.92
127.75
127.42
126.72
126.07
124.91
113.69
112.65
56.28
40.15
39.94
39.73
39.52
39.31
39.11
38.90
^{13}C NMR (100 MHz,d_6-DMSO)
Br
OH
N
SO_2Ph
IA9
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

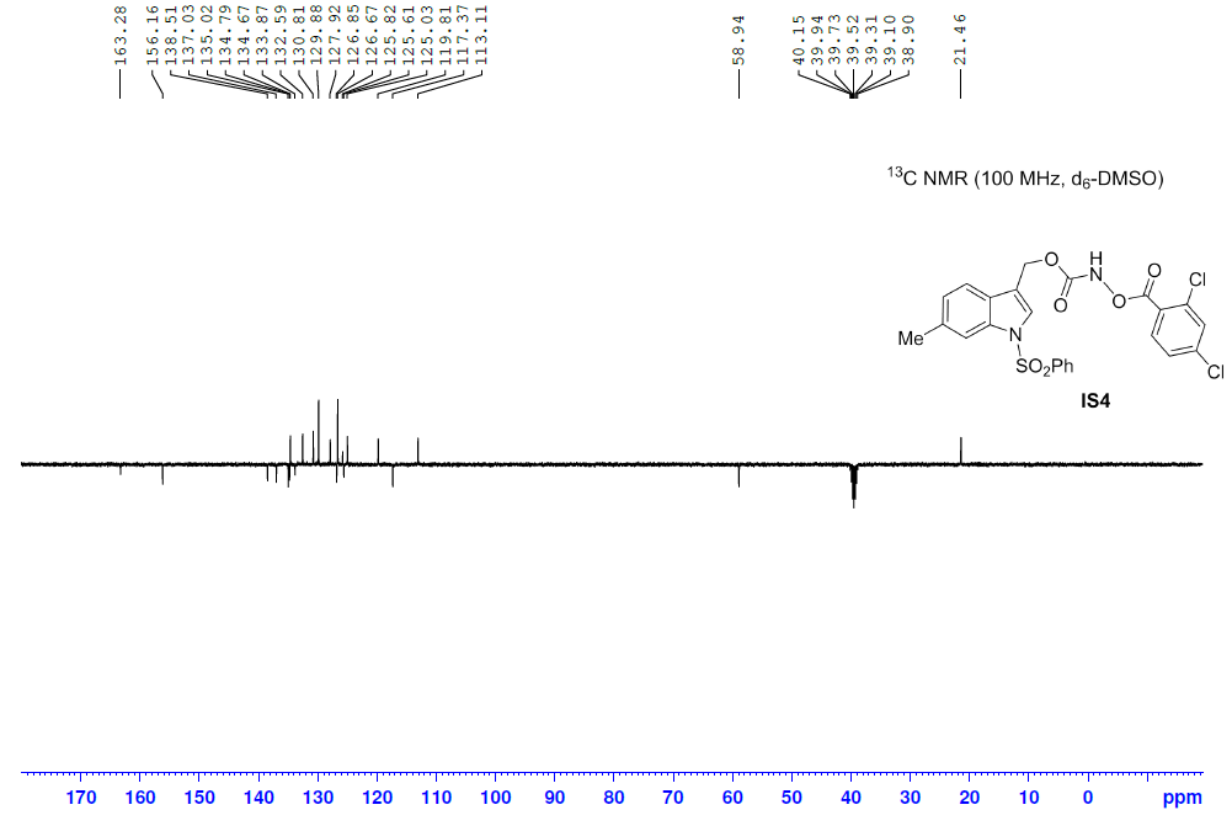

8.534
8.003
7.982
7.912
7.893
7.839
7.818
7.697
7.581
7.562
7.536
7.519
7.500
7.480
7.448
7.430
7.411
7.369
7.350
7.331
7.266
7.246
7.227
5.386
1H NMR (400 MHz, CDCl3)
Cl
Cl
SO2Ph
1
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.05
2.00
1.04
1.04
1.02
1.96
2.05
1.09
2.33
2.01

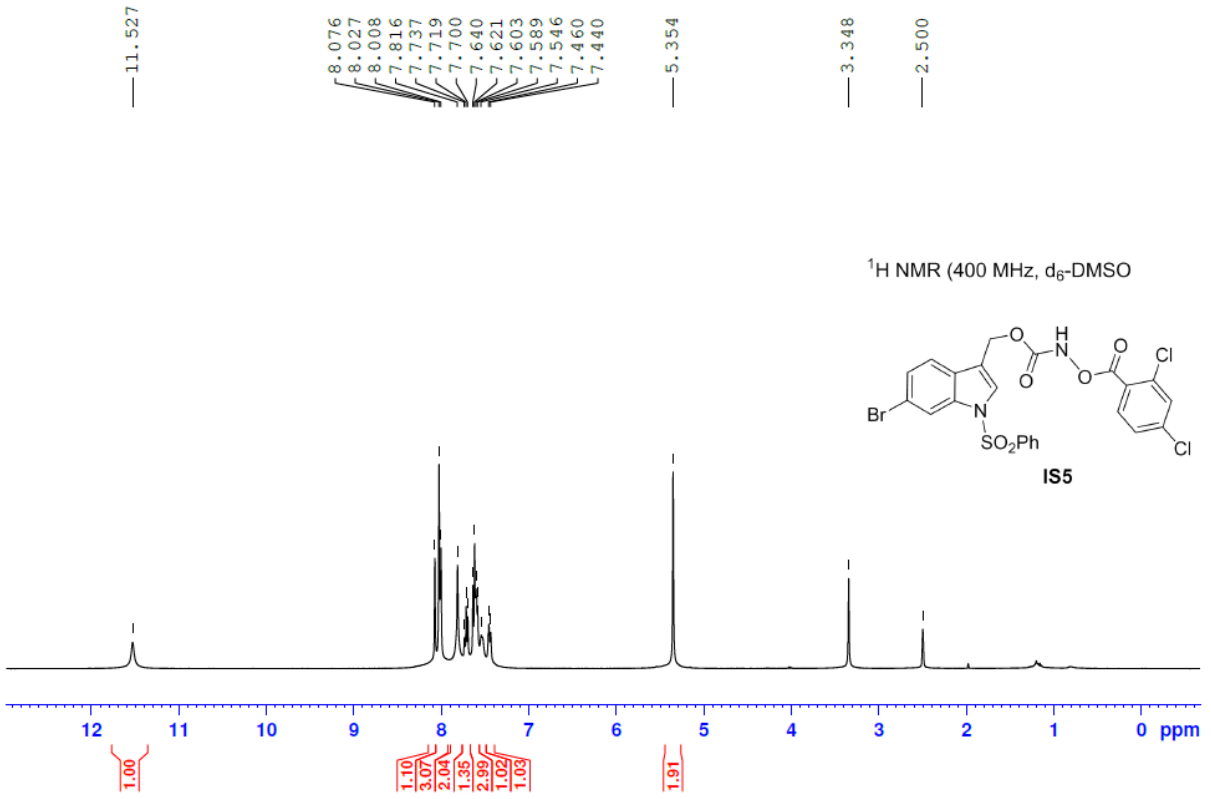

163.64
156.18
139.83
137.85
135.62
134.99
133.94
132.72
131.17
129.29
129.15
127.18
126.76
126.12
125.19
124.52
123.56
119.64
116.47
113.55
77.32
77.00
76.68
60.04
13C NMR (100 MHz, CDCl3)
Cl
Cl
SO2Ph
1
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

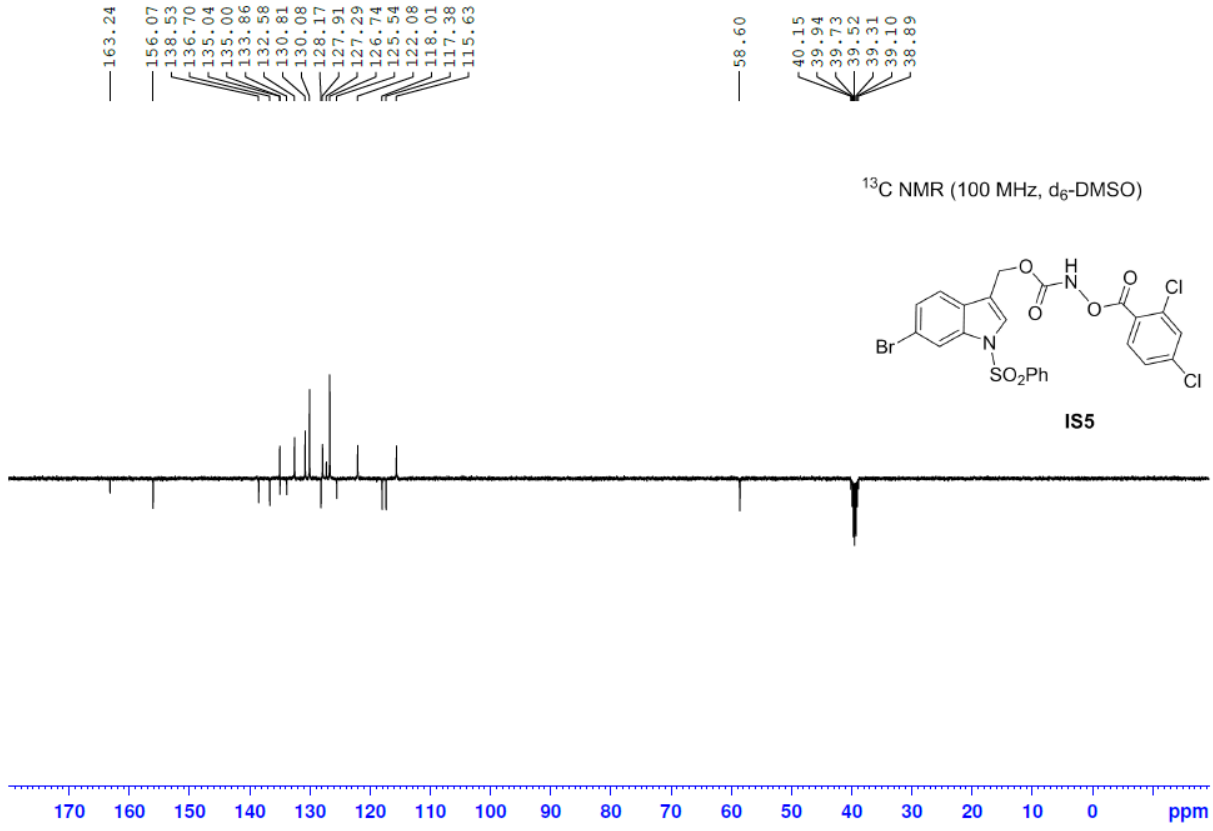

8.411
8.116
7.882
7.859
7.835
7.619
7.527
7.508
7.449
7.430
7.411
7.330
7.260
7.162
7.141
5.351
3.958
2.380
1H NMR (400 MHz, CDCl3)
Me
SO2Ph
CO2Me
IS2
9
8
7
6
5
4
3
2
1
0
ppm
1.00
4.08
3.23
1.09
1.06
2.16
1.05
1.05
2.07
3.22
3.07
165.01
156.20
138.02
135.09
133.95
133.44
133.36
130.27
129.94
129.83
129.50
129.35
126.84
126.71
126.27
119.52
116.36
113.36
77.37
77.05
76.73
60.16
52.65
21.33
13C NMR (100 MHz, CDCl3)
Me
SO2Ph
CO2Me
IS2
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

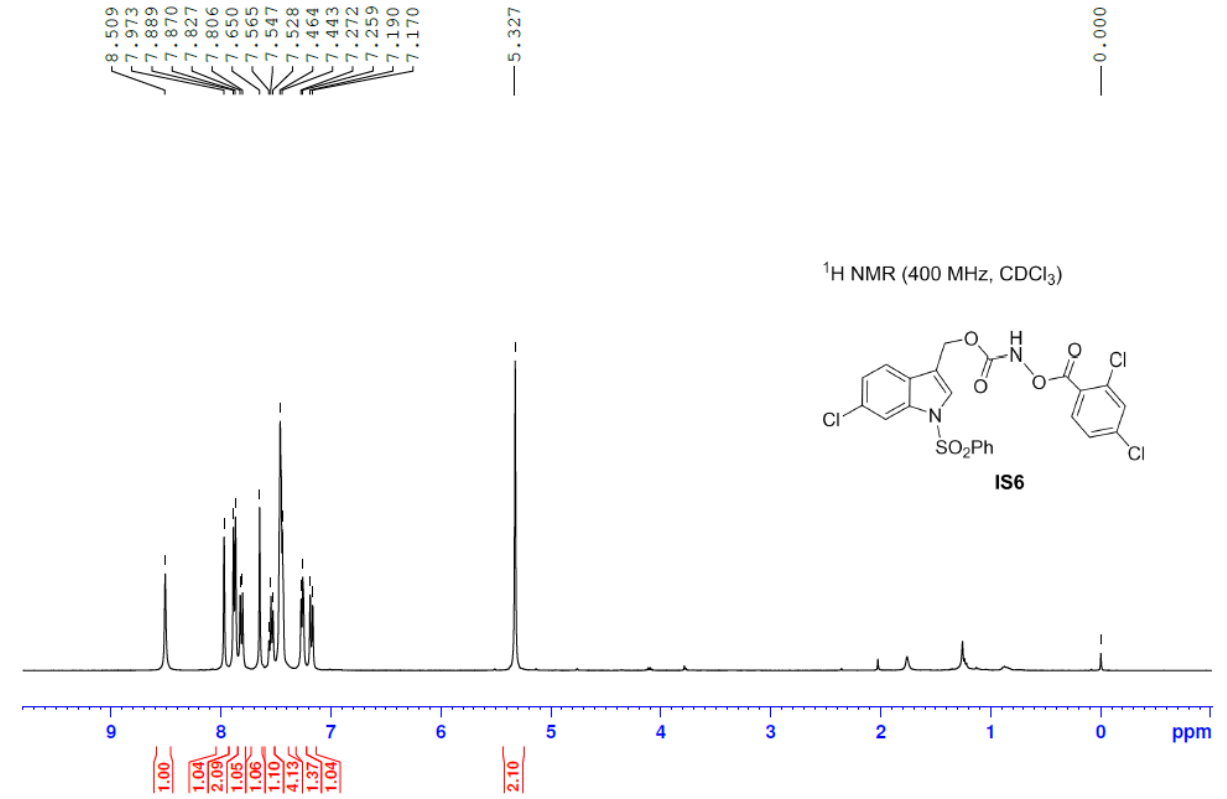

8.371
8.112
7.869
7.848
7.620
7.531
7.513
7.451
7.432
7.413
7.260
6.981
6.955
6.932
5.348
3.959
3.792
^{1}H NMR (400 MHz, CDCl$_3$)
MeO
SO$_2$Ph
CO$_2$Me
IS3
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00 4.27 3.43 1.10 1.12 2.34 0.98 1.05 2.07 3.14 3.09
166.03
165.15
156.84
156.34
138.14
135.26
134.07
130.34
129.39
128.31
126.93
116.71
114.75
114.61
102.04
77.48
77.16
76.84
60.23
55.80
52.75
^{13}C NMR (100 MHz, CDCl$_3$)
MeO
SO$_2$Ph
CO$_2$Me
IS3
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

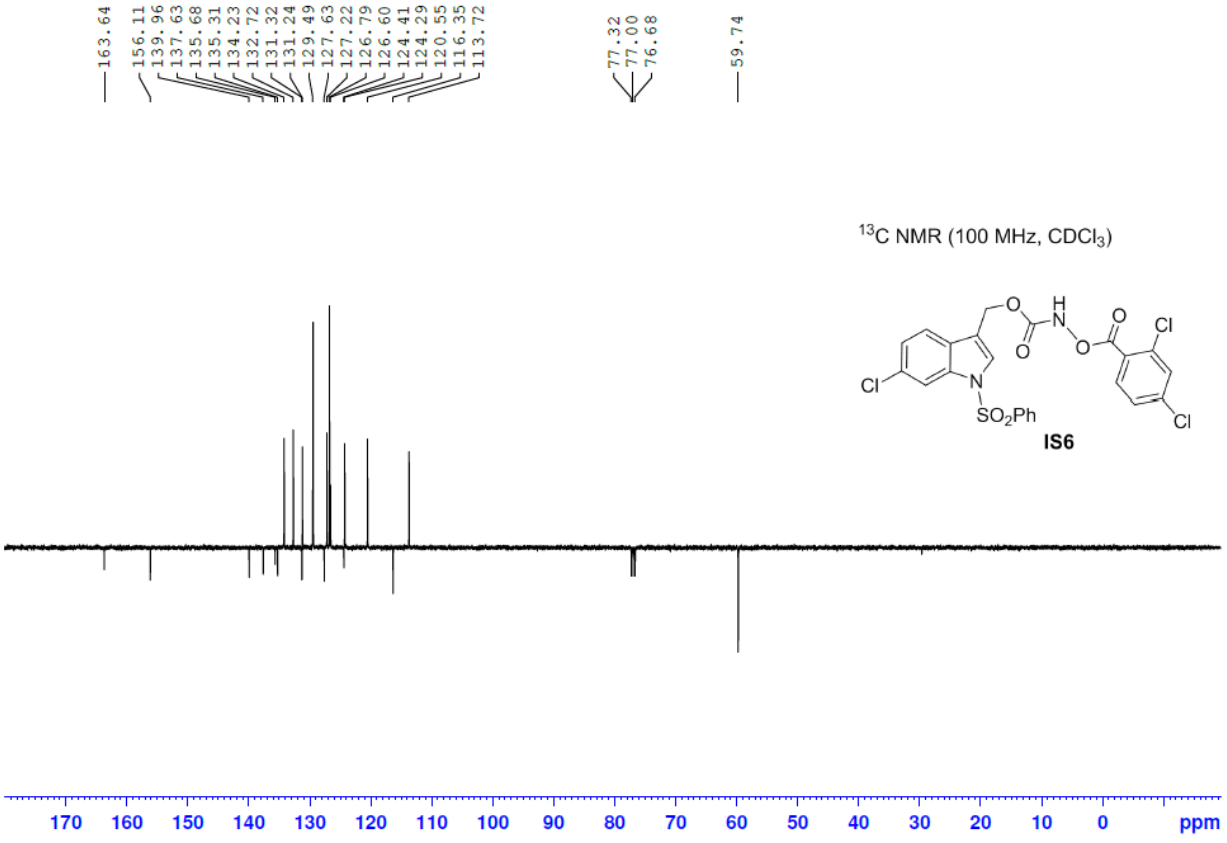

11.517
7.997
7.979
7.875
7.822
7.768
7.697
7.680
7.663
7.604
7.586
7.568
7.506
7.487
7.100
7.082
5.340
3.360
2.500
2.435
1H NMR (400 MHz, d6-DMSO)
Me
N
SO2Ph
O
H
N
O
O
O
O
Cl
Cl
IS4
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
2.11
4.09
1.12
4.04
0.99
2.02
2.95

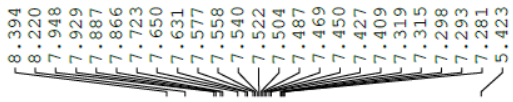

163.28
156.16
138.51
137.03
135.02
134.79
134.67
133.87
132.59
130.81
129.88
127.92
126.85
126.67
125.82
125.61
125.03
119.81
117.37
113.11
58.94
40.15
39.94
39.73
39.52
39.31
39.10
38.90
21.46
13C NMR (100 MHz, d6-DMSO)
Me
N
SO2Ph
O
H
N
O
O
O
O
Cl
Cl
IS4
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


11.527
8.076
8.027
8.008
7.816
7.737
7.719
7.700
7.640
7.621
7.603
7.589
7.546
7.460
7.440
5.354
3.348
2.500
1H NMR (400 MHz, d6-DMSO
IS5
12
11
10
9
8
7
6
5
4
3
2
1
0 ppm
1.00
1.10
3.07
2.04
1.35
2.99
1.02
1.03
1.91

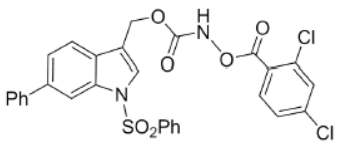

163.24
156.07
138.53
136.70
135.04
135.00
133.86
132.58
130.81
130.08
128.17
127.91
127.29
126.74
125.54
122.08
118.01
117.38
115.63
58.60
40.15
39.94
39.73
39.52
39.31
39.10
38.89
13C NMR (100 MHz, d6-DMSO)
IS5
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


8.509
7.973
7.889
7.870
7.827
7.806
7.650
7.565
7.547
7.528
7.464
7.443
7.272
7.259
7.190
7.170
5.327
0.000
1H NMR (400 MHz, CDCl3)
IS6
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.04
2.09
1.05
1.06
1.10
4.13
1.37
1.04
2.10

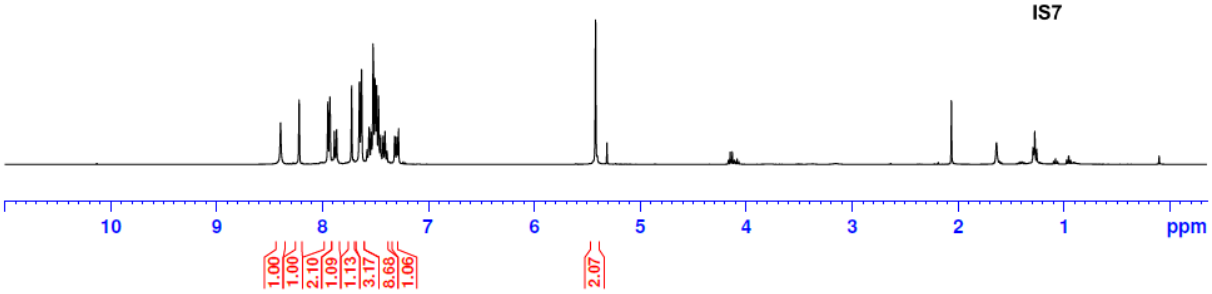

163.64
156.11
139.96
137.63
135.68
135.31
134.23
132.72
131.32
131.24
129.49
127.63
127.22
126.79
126.60
124.41
124.29
120.55
116.35
113.72
77.32
77.00
76.68
59.74
13C NMR (100 MHz, CDCl3)
IS6
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

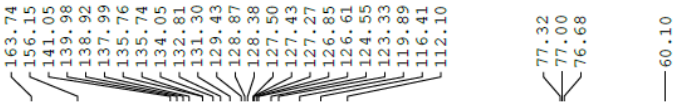


^{1}H NMR (400 MHz, $CDCl_3$)

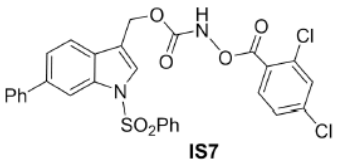


IS7

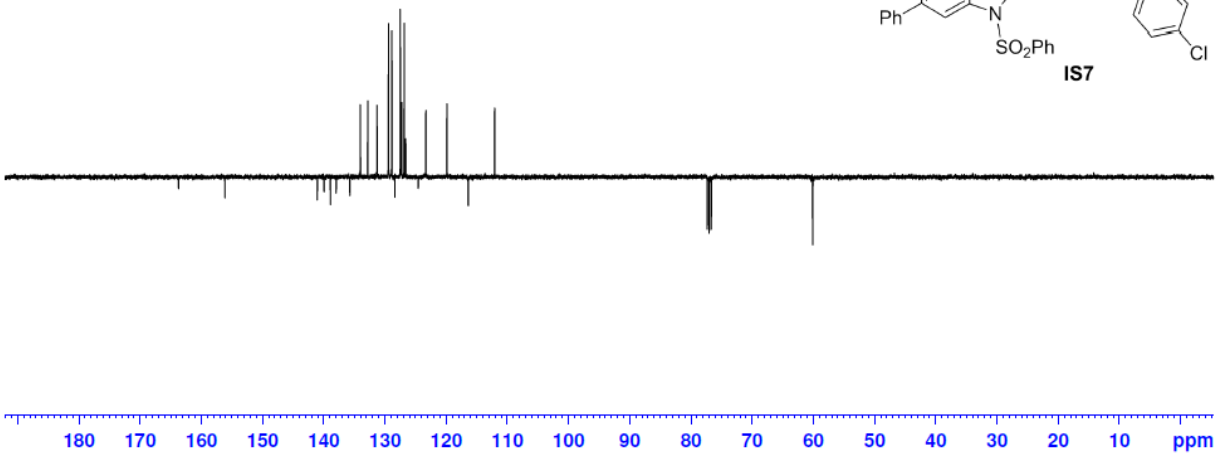


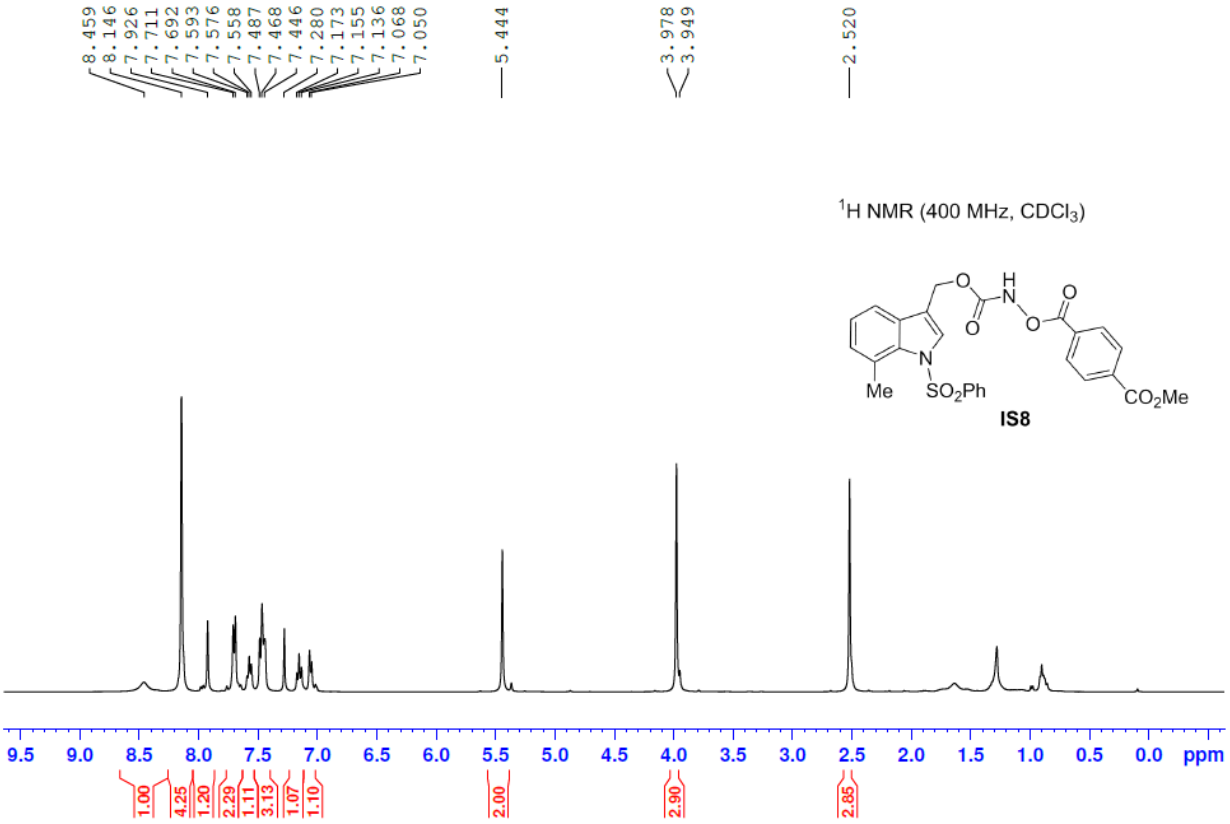


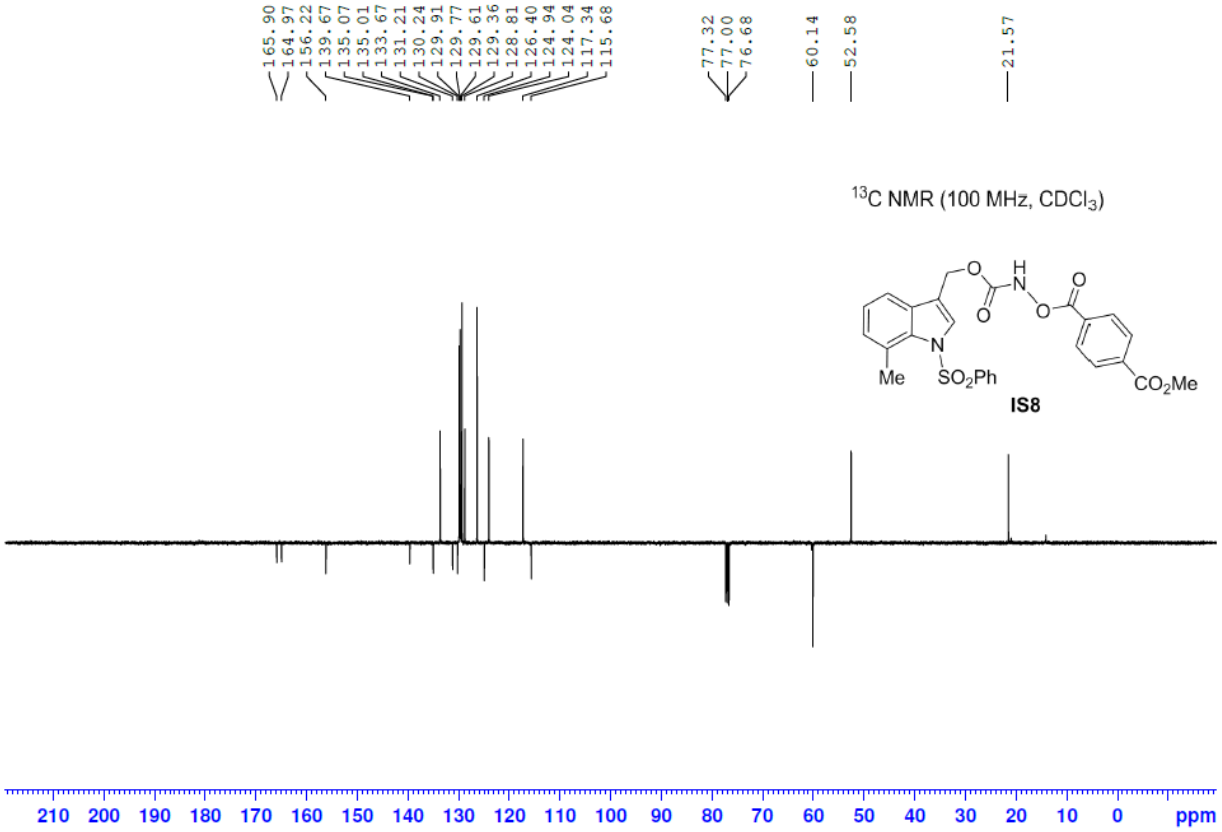
^{13}C NMR (100 MHz, $CDCl_3$)

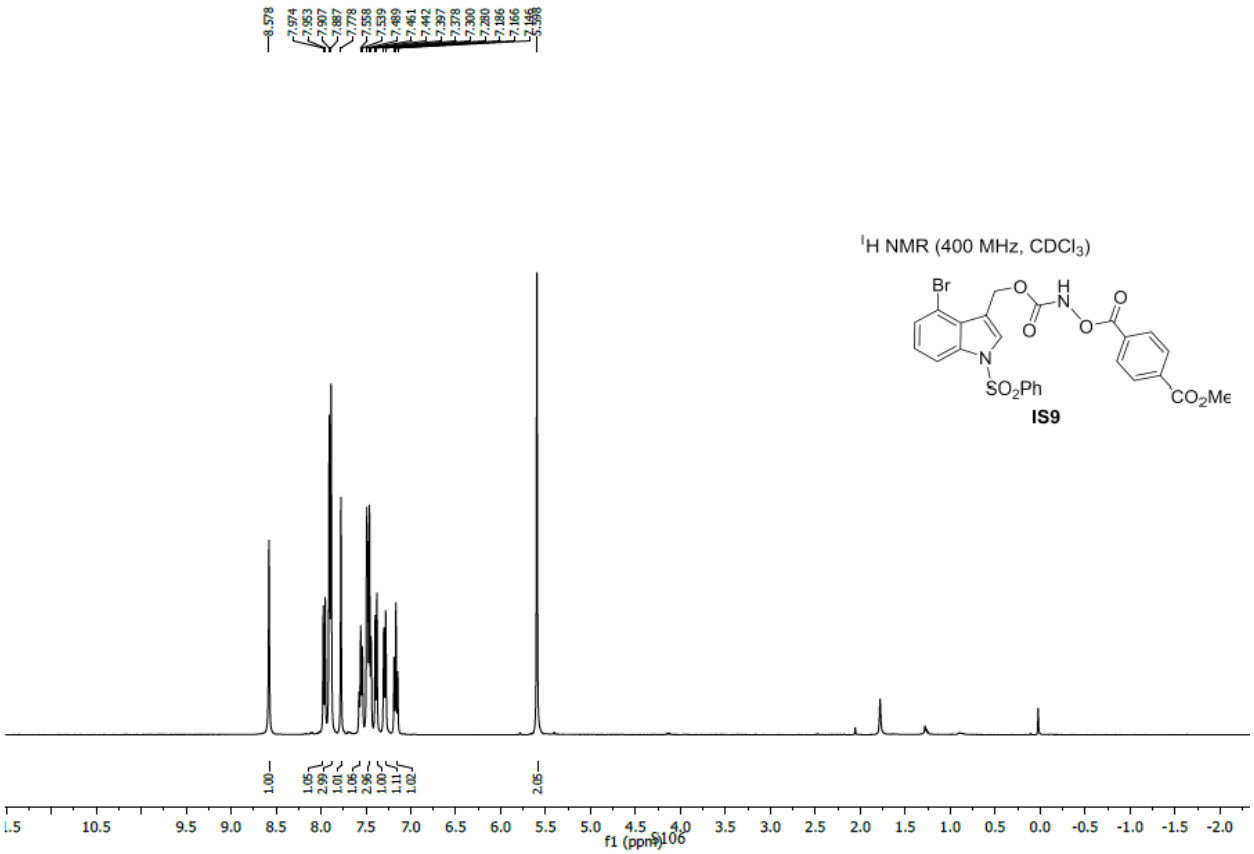


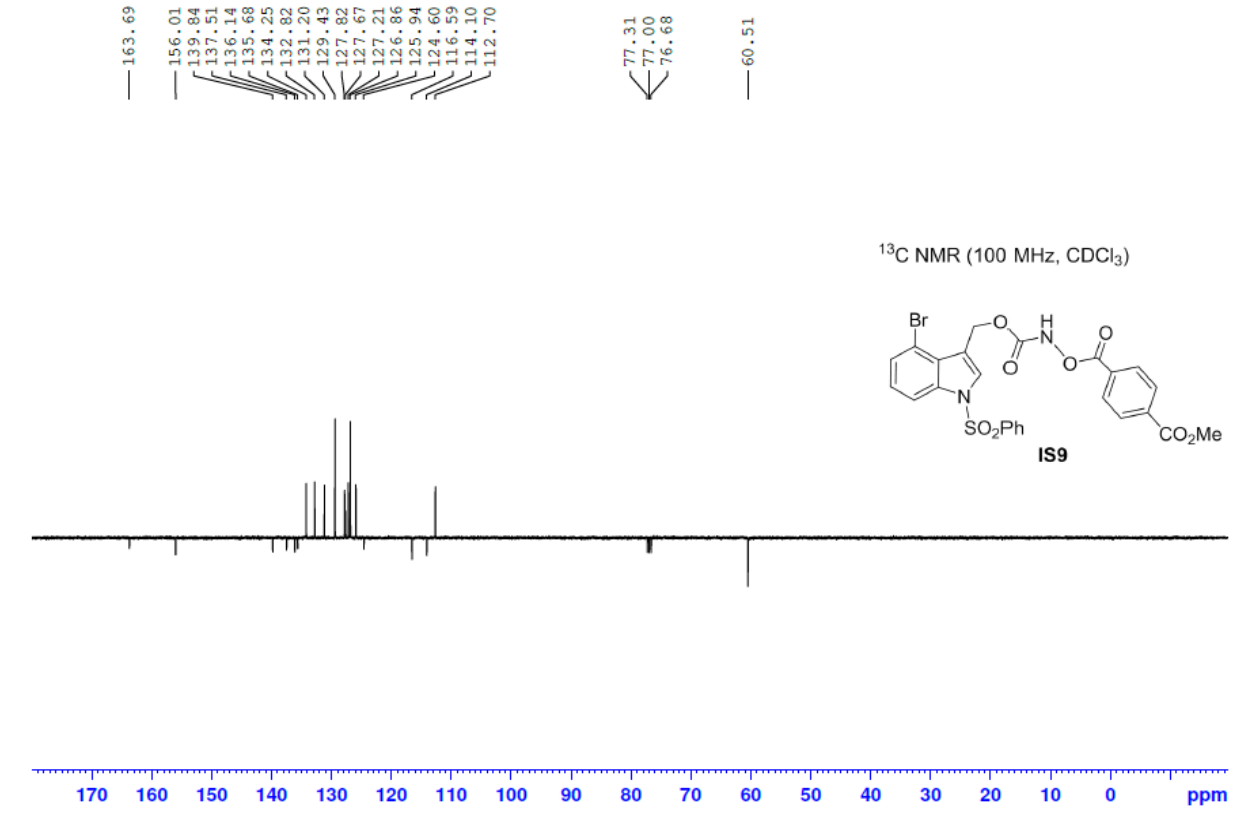
IS7

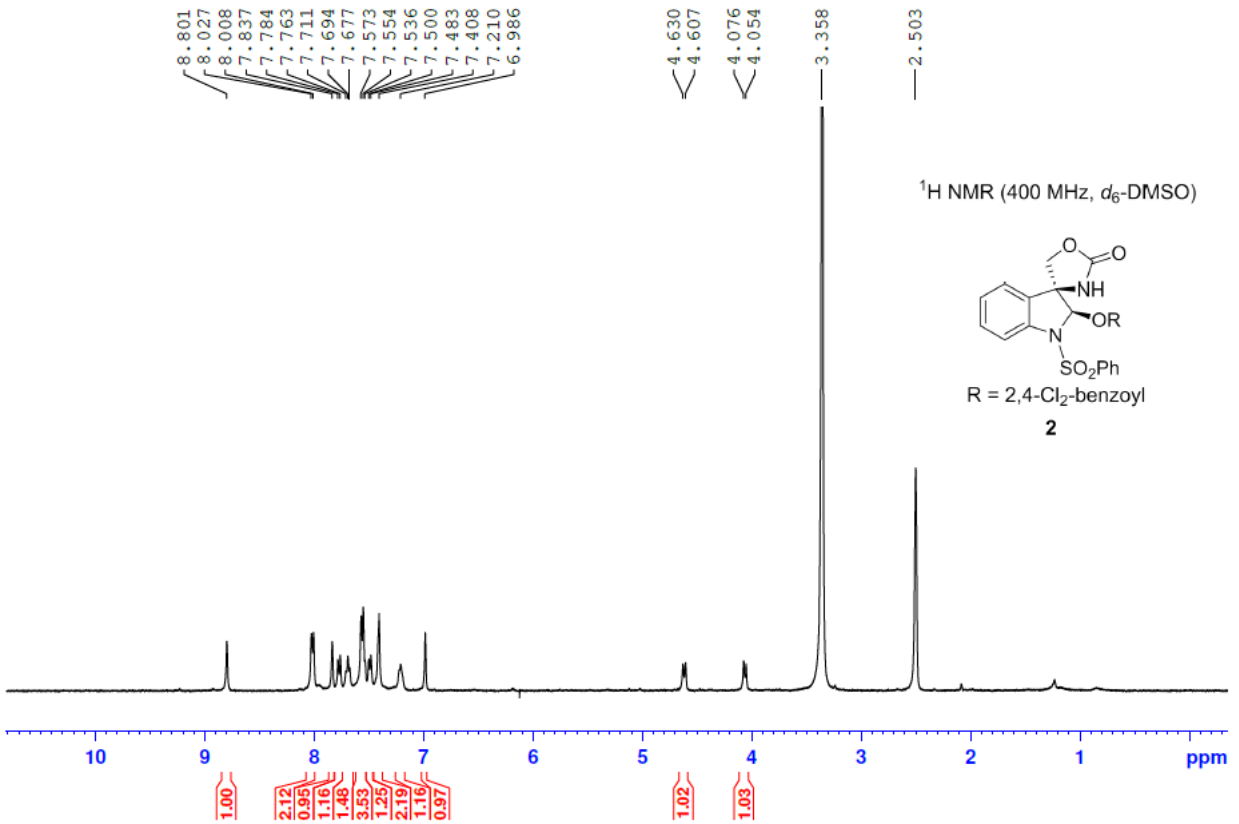



8.459
8.146
7.926
7.711
7.692
7.593
7.576
7.558
7.487
7.468
7.446
7.280
7.173
7.155
7.136
7.068
7.050
5.444
3.978
3.949
2.520
1H NMR (400 MHz, CDCl3)
Me
SO2Ph
CO2Me
IS8
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.00
4.25
1.20
2.29
1.11
3.13
1.07
1.10
2.00
2.90
2.85


165.90
164.97
156.22
139.67
135.07
135.01
133.67
131.21
130.24
129.91
129.77
129.61
129.36
128.81
126.40
124.94
124.04
117.34
115.68
77.32
77.00
76.68
60.14
52.58
21.57
13C NMR (100 MHz, CDCl3)
Me
SO2Ph
CO2Me
IS8
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


8.578
7.974
7.953
7.907
7.887
7.778
7.558
7.539
7.489
7.461
7.442
7.397
7.378
7.300
7.280
7.186
7.166
5.398
^{1}H NMR (400 MHz, $CDCl_3$)
Br
O
H
N
O
O
O
N
SO_2Ph
CO_2Me
IS9
1.00
1.05
2.99
1.01
1.05
2.96
1.00
1.11
1.02
2.05
f1 (ppm)

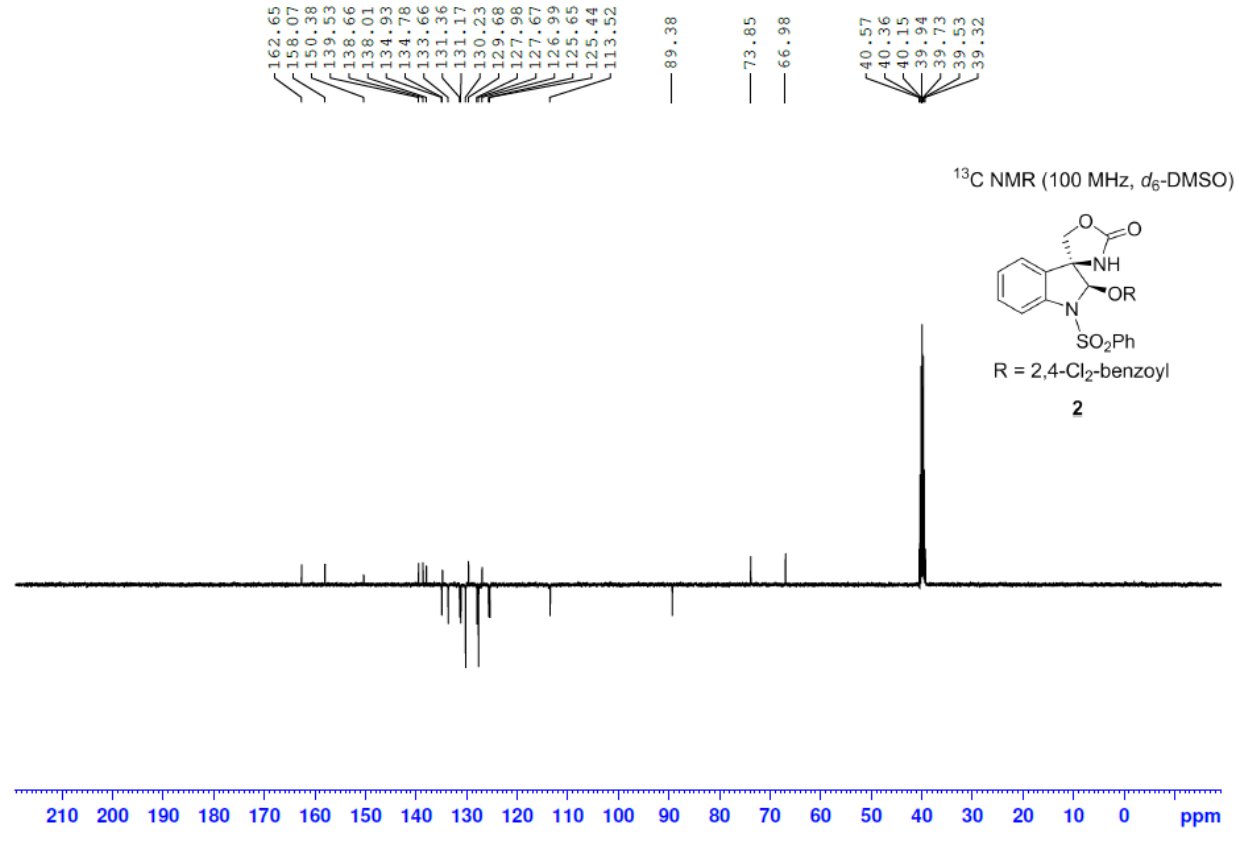

163.69
156.01
139.84
137.51
136.14
135.68
134.25
132.82
131.20
129.43
127.82
127.67
127.21
126.86
125.94
124.60
116.59
114.10
112.70
77.31
77.00
76.68
60.51
^{13}C NMR (100 MHz, $CDCl_3$)
Br
O
H
N
O
O
O
N
SO_2Ph
CO_2Me
IS9
ppm



^{1}H NMR (400 MHz, d_6-DMSO)

R = 2,4-Cl_2-benzoyl

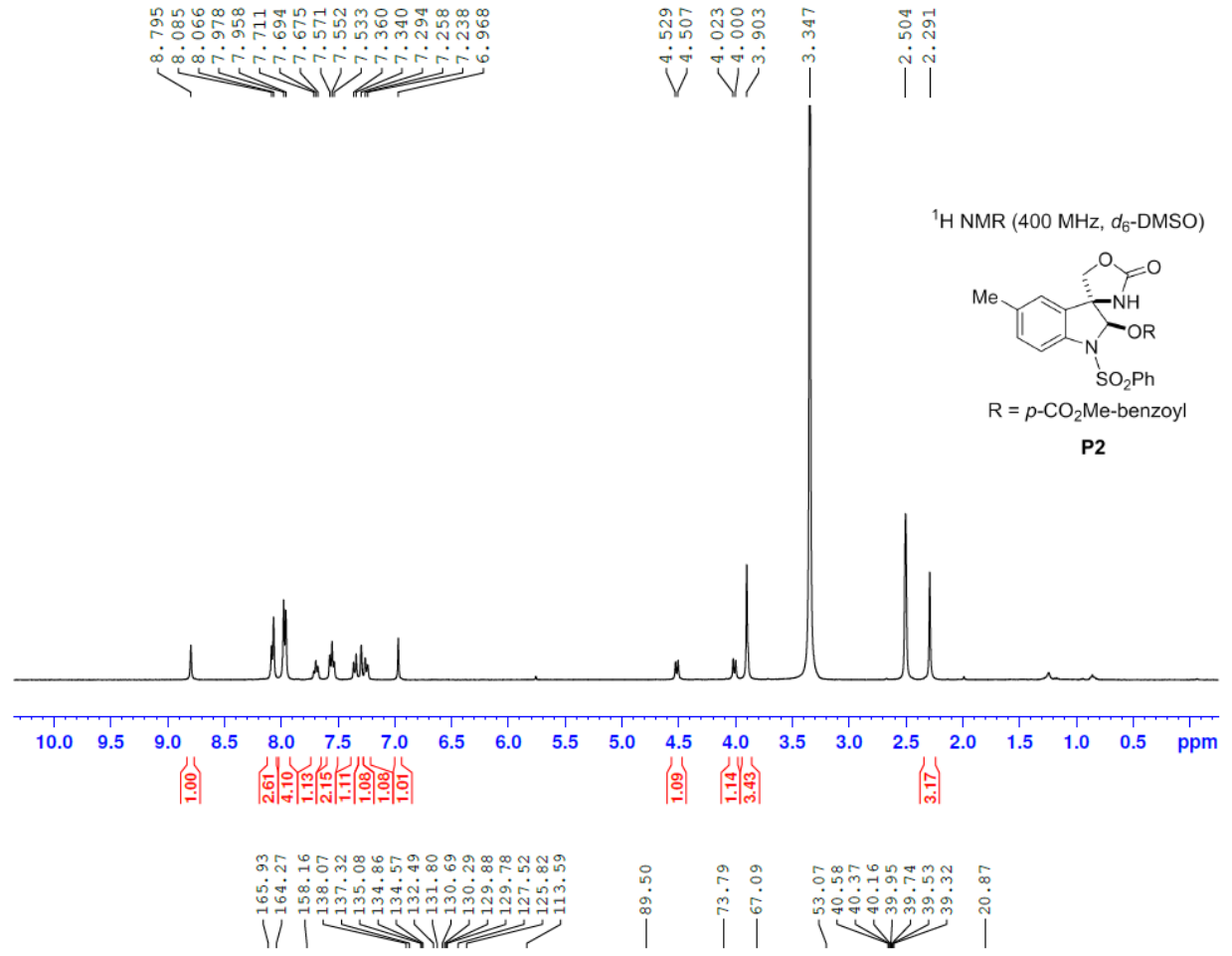
2



^{13}C NMR (100 MHz, d_6-DMSO)

R = 2,4-Cl_2-benzoyl

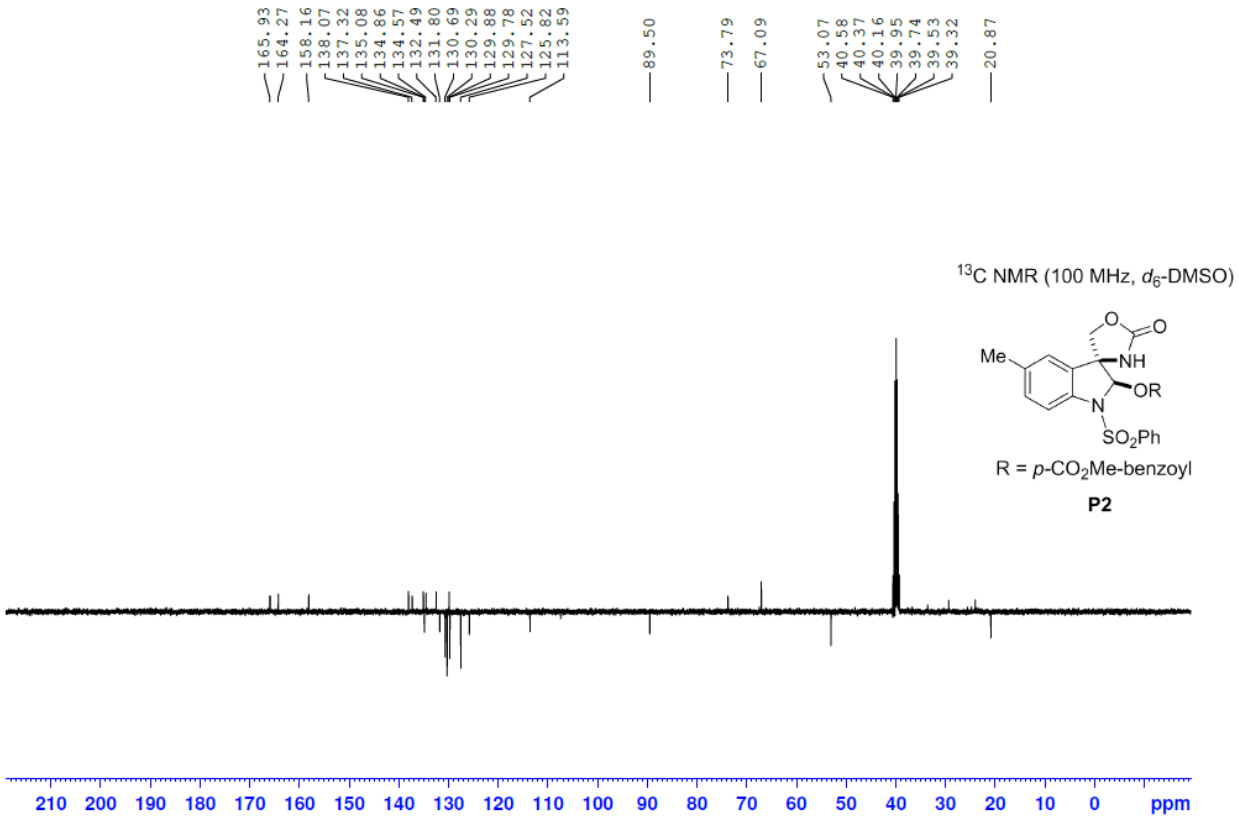
2



^{1}H NMR (400 MHz, d_6-DMSO)

R = *p*-CO_2Me-benzoyl

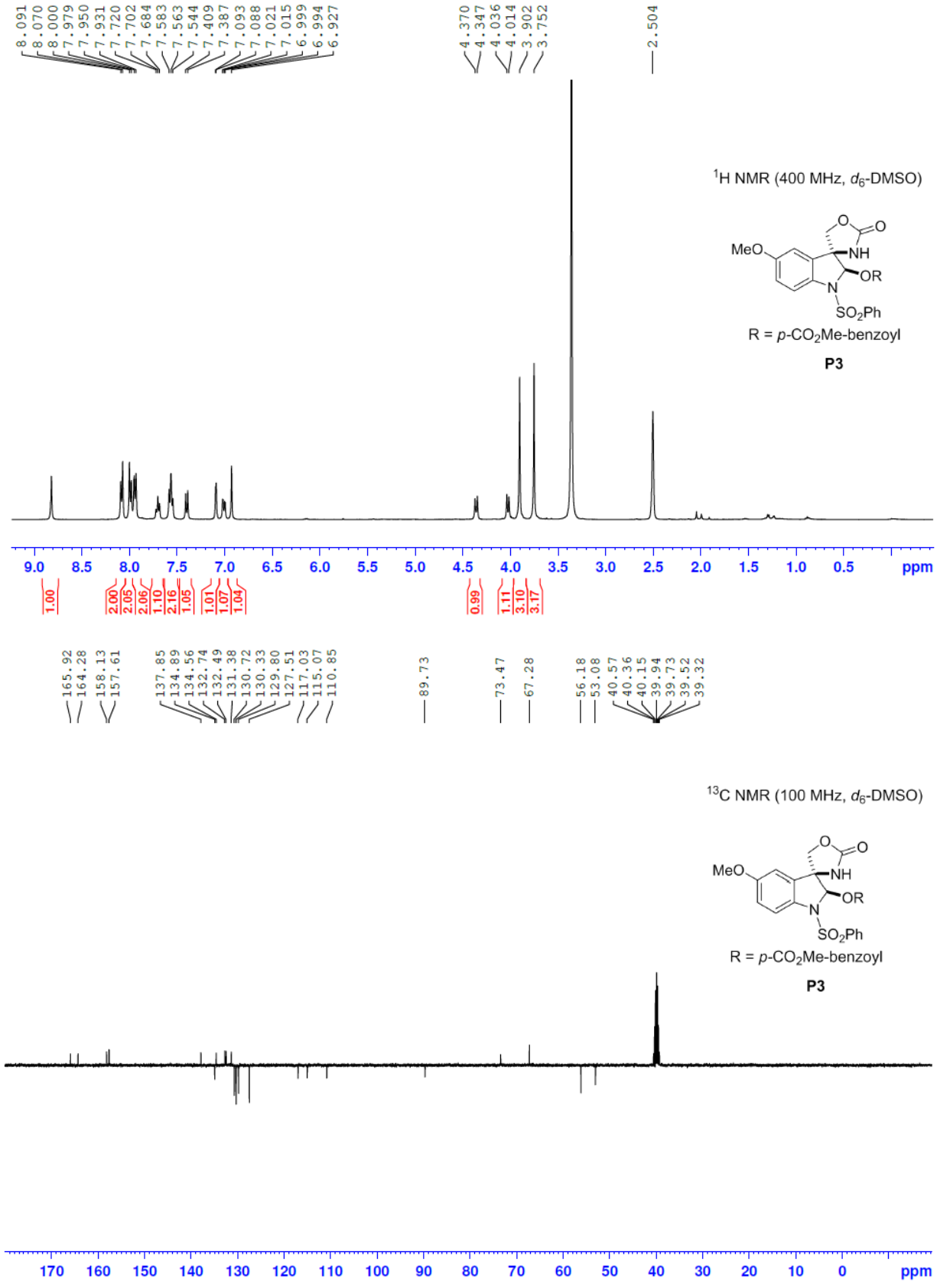
P2

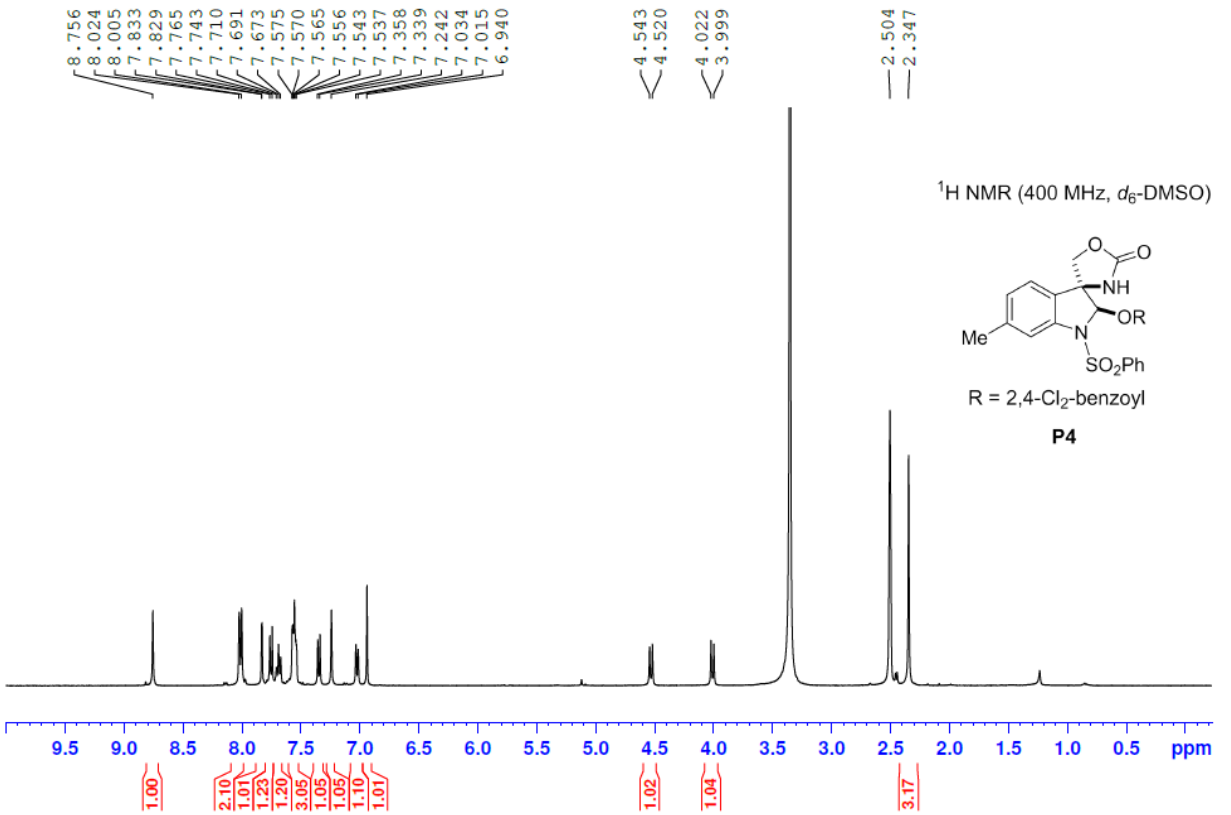


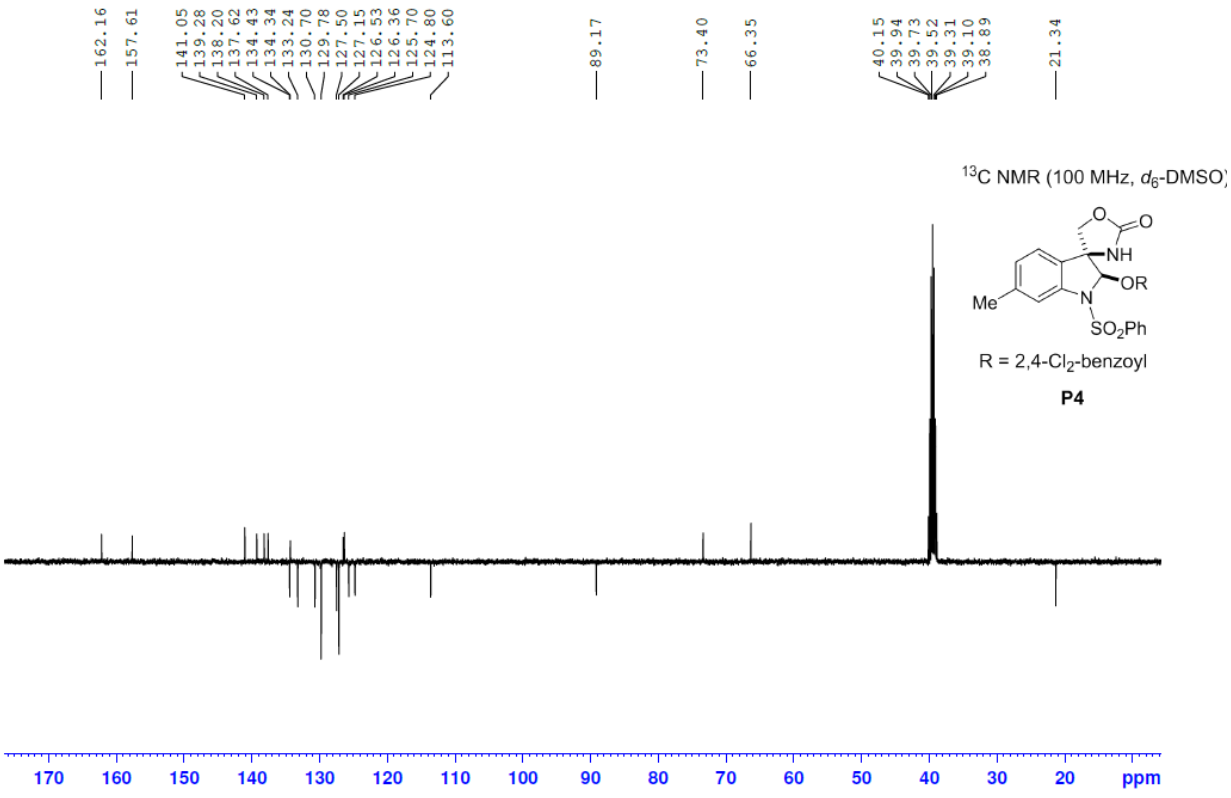
^{13}C NMR (100 MHz, d_6-DMSO)

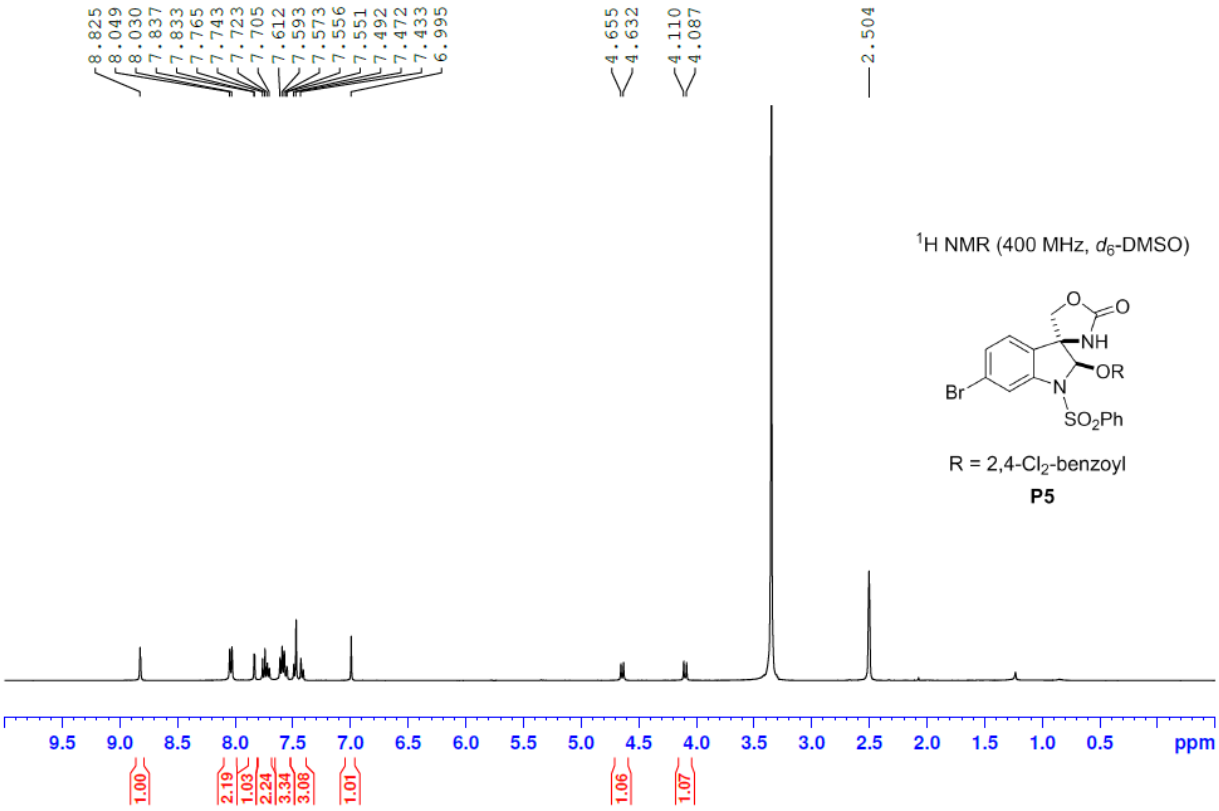
R = *p*-CO_2Me-benzoyl

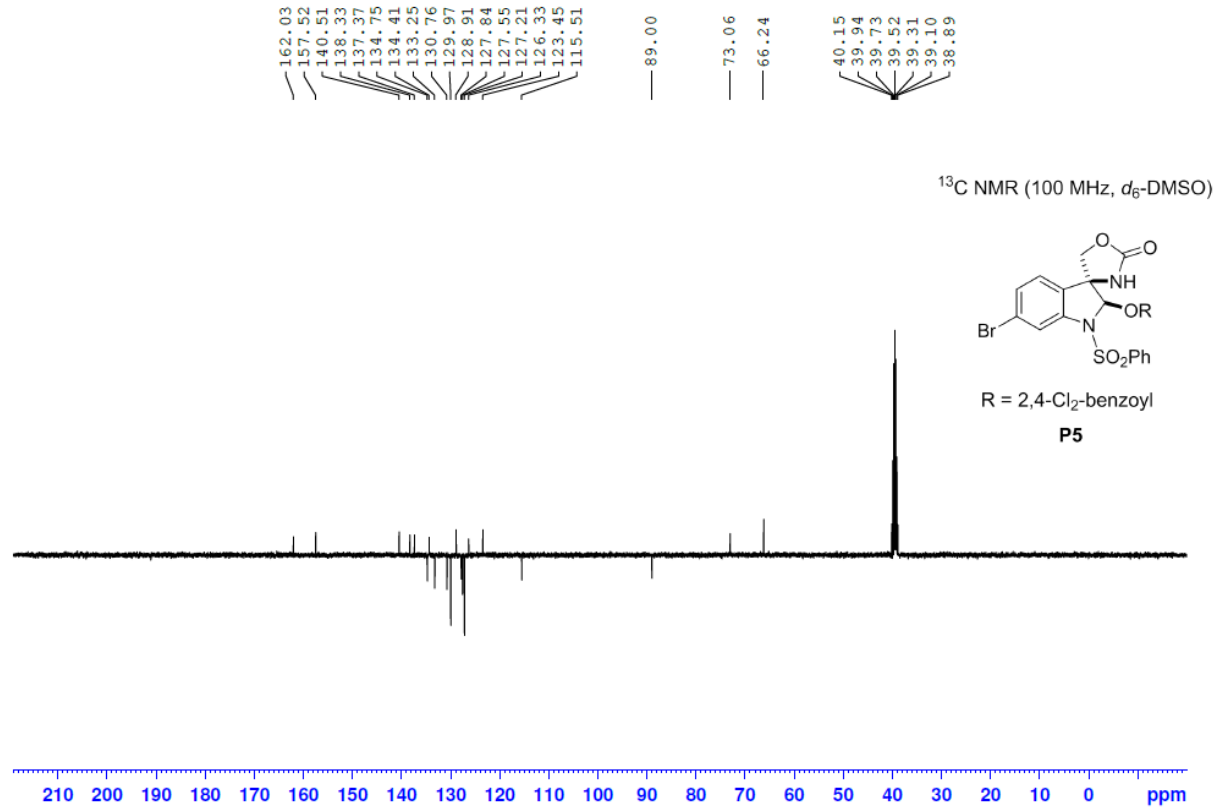
P2

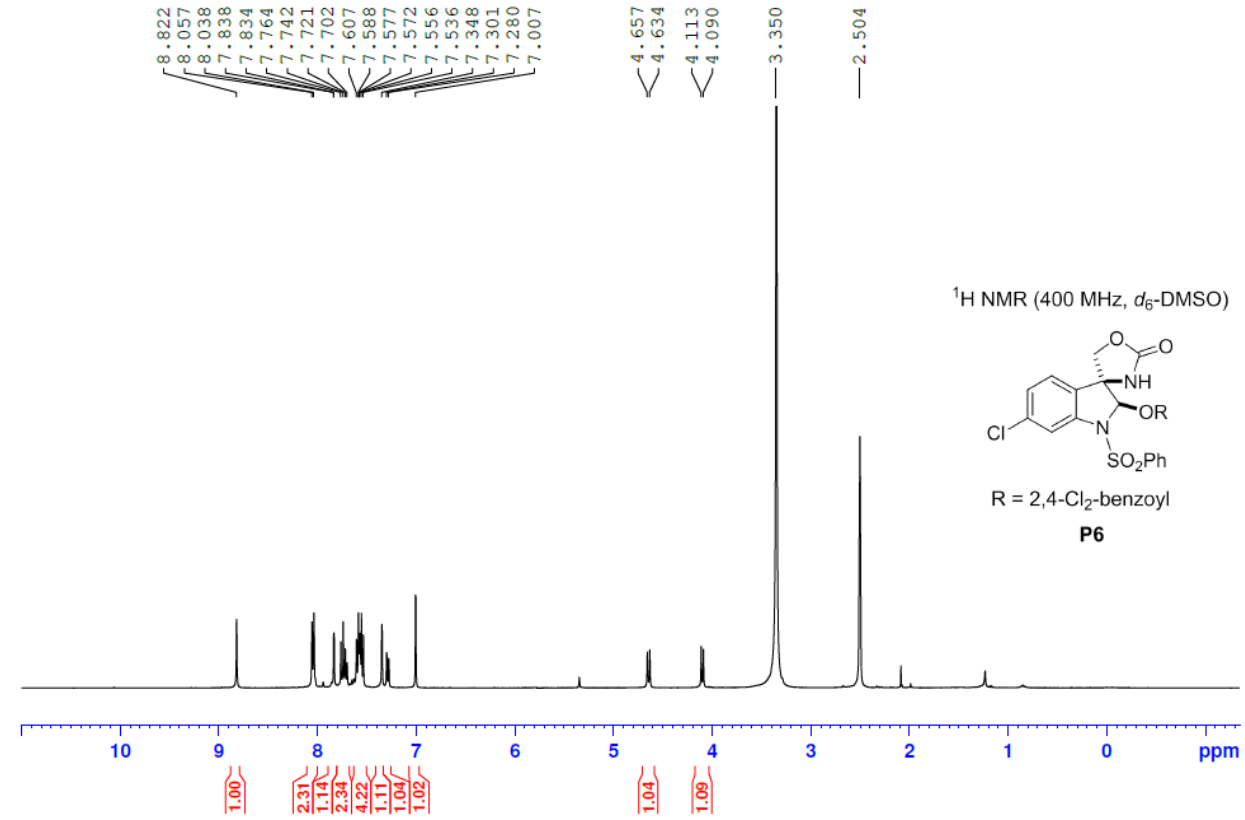

8.091
8.070
8.000
7.979
7.950
7.931
7.720
7.702
7.684
7.583
7.563
7.544
7.409
7.387
7.093
7.088
7.021
7.015
6.999
6.994
6.927
4.370
4.347
4.036
4.014
3.902
3.752
2.504
1H NMR (400 MHz, d6-DMSO)
MeO
NH
OR
N
SO2Ph
R = p-CO2Me-benzoyl
P3
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
2.00
2.05
2.06
1.10
2.16
1.05
1.01
1.07
1.04
0.99
1.11
3.10
3.17
165.92
164.28
158.13
157.61
137.85
134.89
134.56
132.74
132.49
131.38
130.72
130.33
129.80
127.51
117.03
115.07
110.85
89.73
73.47
67.28
56.18
53.08
40.57
40.36
40.15
39.94
39.73
39.52
39.32
13C NMR (100 MHz, d6-DMSO)
MeO
NH
OR
N
SO2Ph
R = p-CO2Me-benzoyl
P3
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


8.756
8.024
8.005
7.833
7.829
7.765
7.743
7.710
7.691
7.673
7.575
7.570
7.565
7.556
7.543
7.537
7.358
7.339
7.242
7.034
7.015
6.940
4.543
4.520
4.022
3.999
2.504
2.347
1H NMR (400 MHz, d6-DMSO)
O
O
NH
OR
N
Me
SO2Ph
R = 2,4-Cl2-benzoyl
P4
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
2.10
1.01
1.23
1.20
3.05
1.05
1.10
1.01
1.02
1.04
3.17


162.16
157.61
141.05
139.28
138.20
137.62
134.43
134.34
133.24
130.70
129.78
127.50
127.15
126.53
126.36
125.70
124.80
113.60
89.17
73.40
66.35
40.15
39.94
39.73
39.52
39.31
39.10
38.89
21.34
13C NMR (100 MHz, d6-DMSO)
O
O
NH
OR
N
Me
SO2Ph
R = 2,4-Cl2-benzoyl
P4
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


8.825
8.049
8.030
7.837
7.833
7.765
7.743
7.723
7.705
7.612
7.593
7.573
7.556
7.551
7.492
7.472
7.433
6.995
4.655
4.632
4.110
4.087
2.504
1H NMR (400 MHz, d6-DMSO)
O
O
NH
OR
Br
N
SO2Ph
R = 2,4-Cl2-benzoyl
P5
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
2.19
1.03
2.24
3.34
3.08
1.01
1.06
1.07

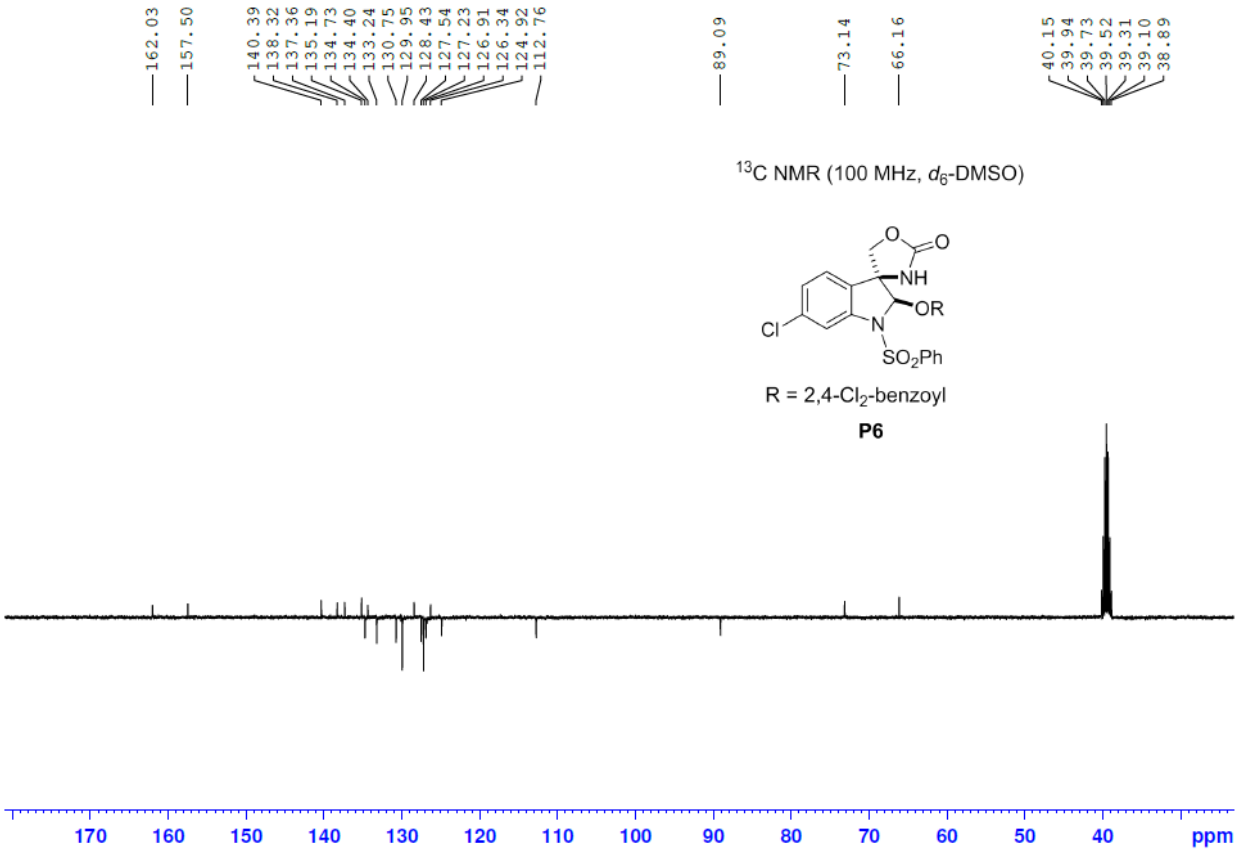

162.03
157.52
140.51
138.33
137.37
134.75
134.41
133.25
130.76
129.97
128.91
127.84
127.55
127.21
126.33
123.45
115.51
89.00
73.06
66.24
40.15
39.94
39.73
39.52
39.31
39.10
38.89
13C NMR (100 MHz, d6-DMSO)
O
O
NH
OR
Br
N
SO2Ph
R = 2,4-Cl2-benzoyl
P5
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



^{1}H NMR (400 MHz, d_6-DMSO)

R = 2,4-Cl_2-benzoyl

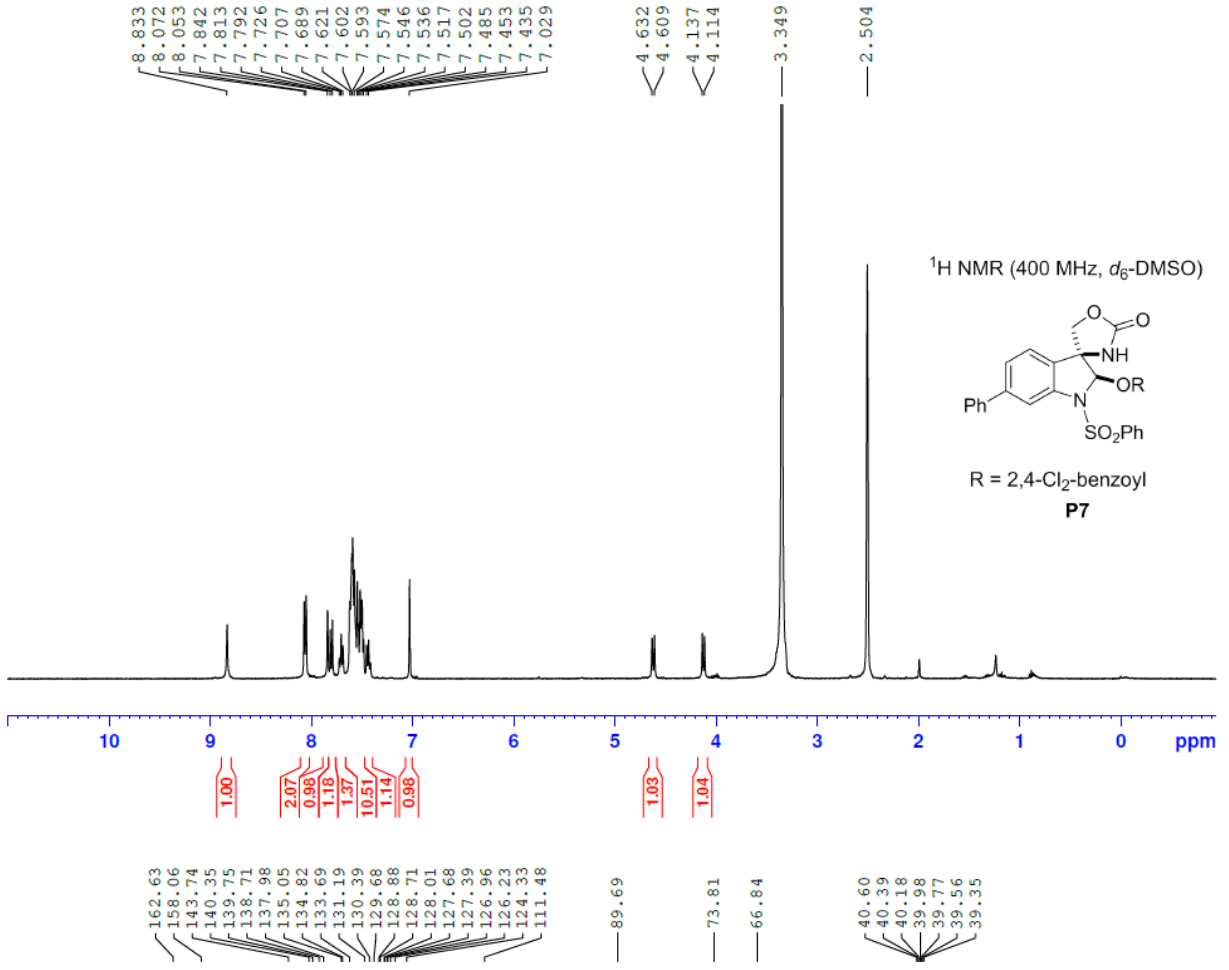
P6



^{13}C NMR (100 MHz, d_6-DMSO)

R = 2,4-Cl_2-benzoyl

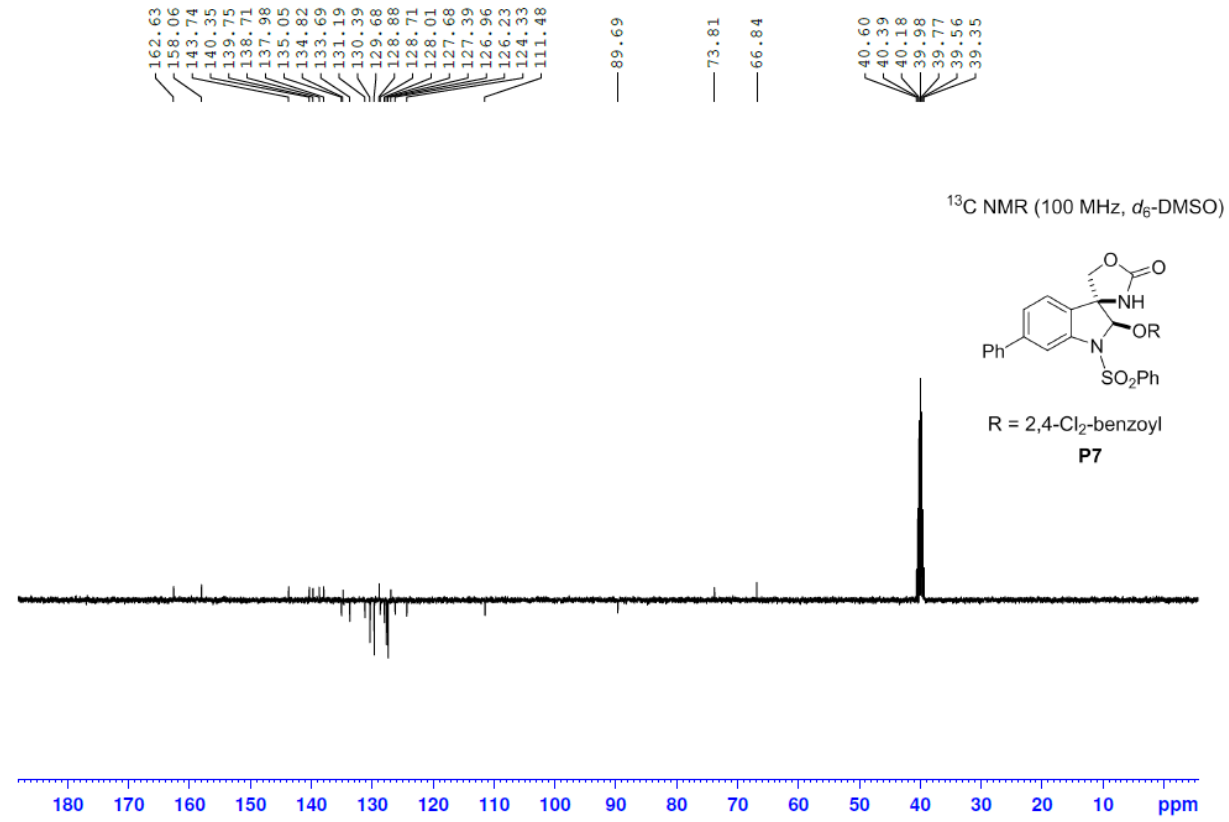
P6



^{1}H NMR (400 MHz, d_6-DMSO)

R = 2,4-Cl_2-benzoyl

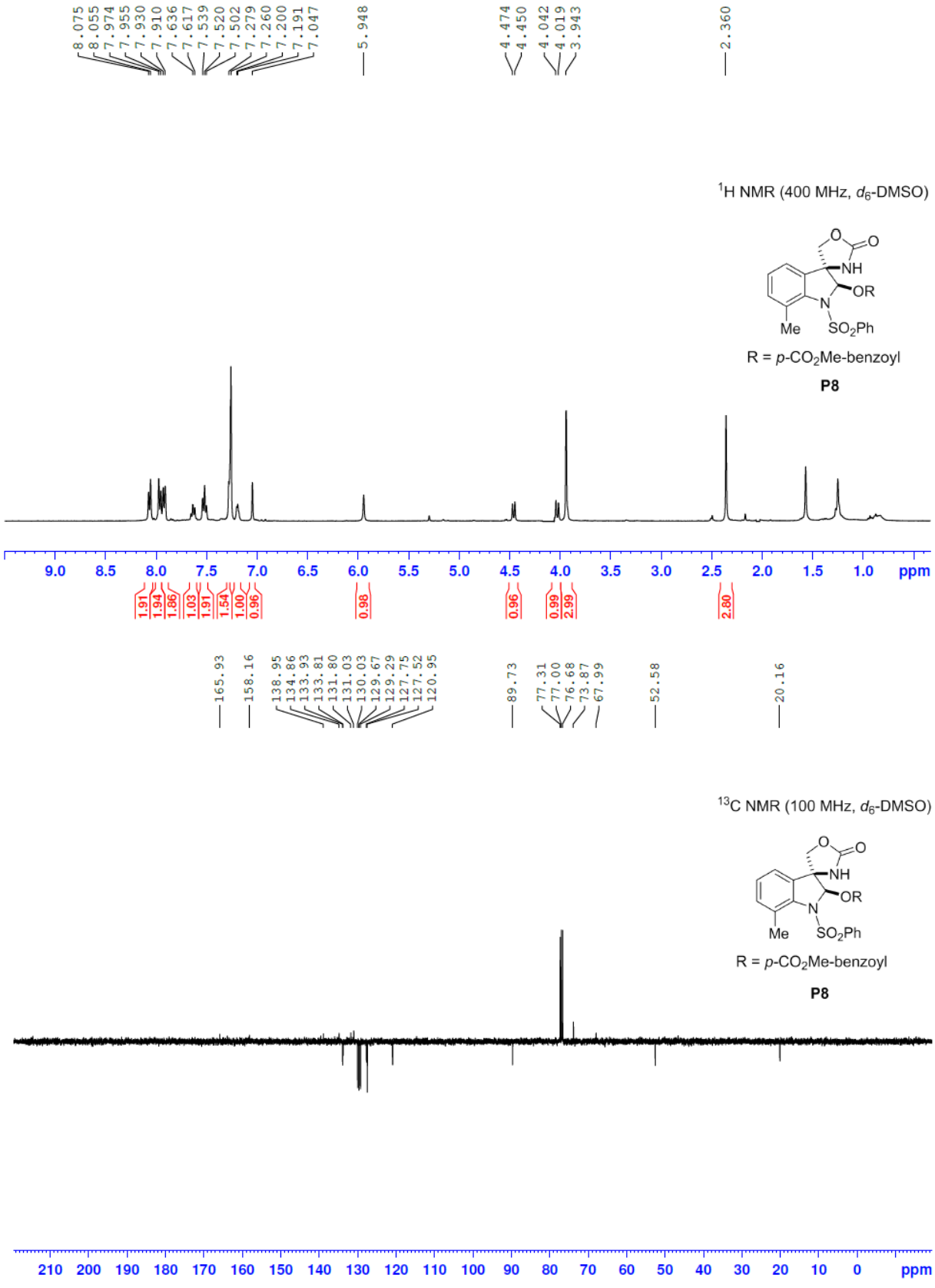
P7



^{13}C NMR (100 MHz, d_6-DMSO)

R = 2,4-Cl_2-benzoyl

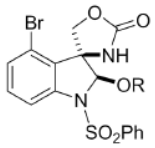
P7


8.075
8.055
7.974
7.955
7.930
7.910
7.636
7.617
7.539
7.520
7.502
7.279
7.260
7.200
7.191
7.047
5.948
4.474
4.450
4.042
4.019
3.943
2.360
^{1}H NMR (400 MHz, d_6-DMSO)
O
O
NH
OR
N
Me
SO_2Ph
R = p-CO_2Me-benzoyl
P8
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.91 1.94 1.86 1.03 1.91 1.54 1.00 0.96 0.98 0.96 0.99 2.99 2.80
165.93
158.16
138.95
134.86
133.93
133.81
131.80
131.03
130.03
129.67
129.29
127.75
127.52
120.95
89.73
77.31
77.00
76.68
73.87
67.99
52.58
20.16
^{13}C NMR (100 MHz, d_6-DMSO)
O
O
NH
OR
N
Me
SO_2Ph
R = p-CO_2Me-benzoyl
P8
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

7.860
7.840
7.729
7.708
7.664
7.644
7.619
7.600
7.501
7.482
7.462
7.353
7.334
7.325
7.305
7.283
7.267
6.810
6.215

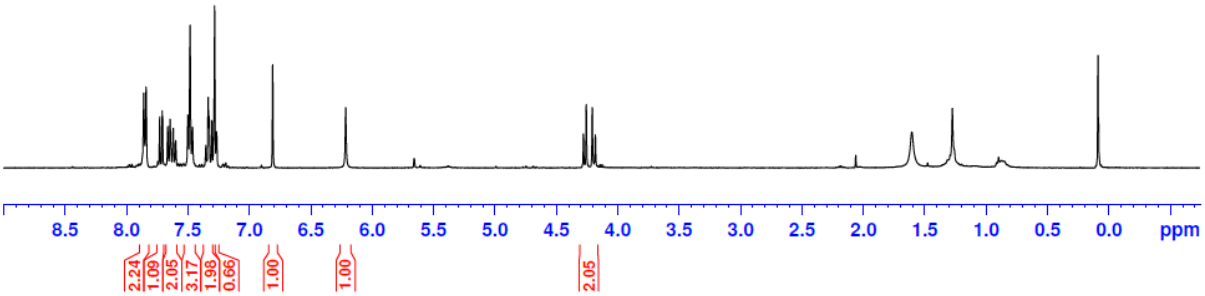
4.282
4.258
4.208
4.185

^{1}H NMR (400 MHz, d_6-DMSO)



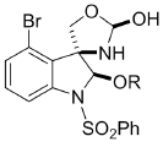
R = 2,4-Cl_2-benzoyl

P9



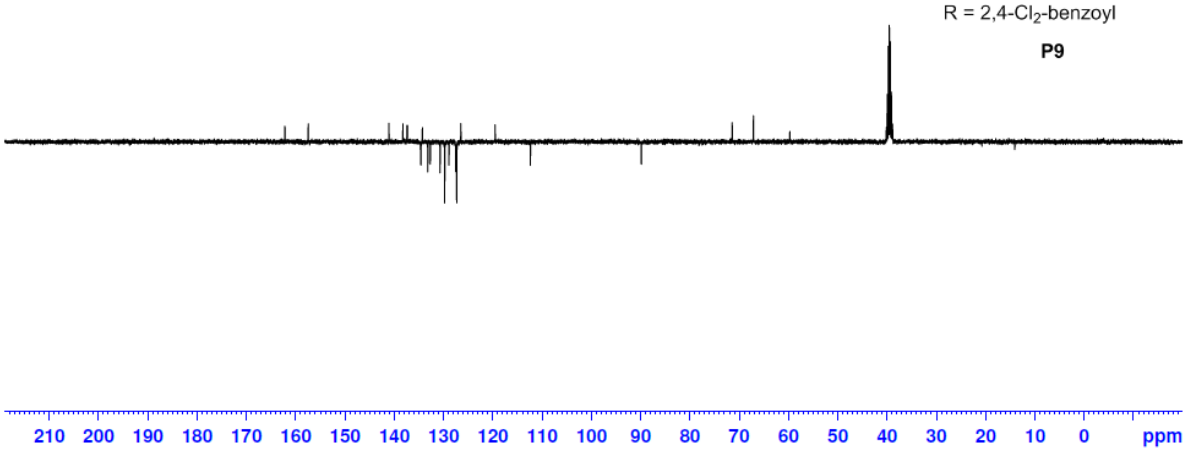
162.20
157.47
141.10
138.25
137.36
134.62
134.20
133.20
132.69
130.72
129.79
128.92
127.53
127.34
126.52
126.48
119.55
112.39
89.85
71.42
67.12
40.14
39.94
39.73
39.52
39.31
39.10
38.89

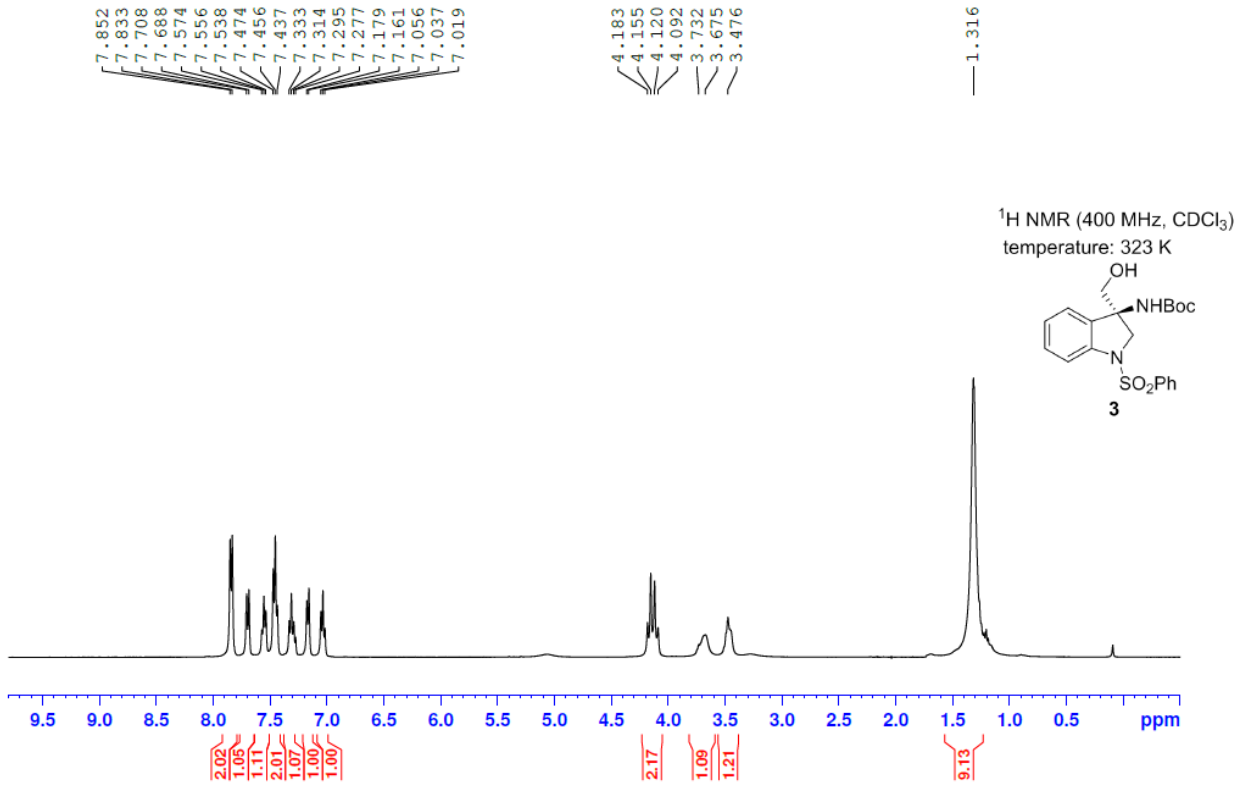
^{13}C NMR (100 MHz, d_6-DMSO)

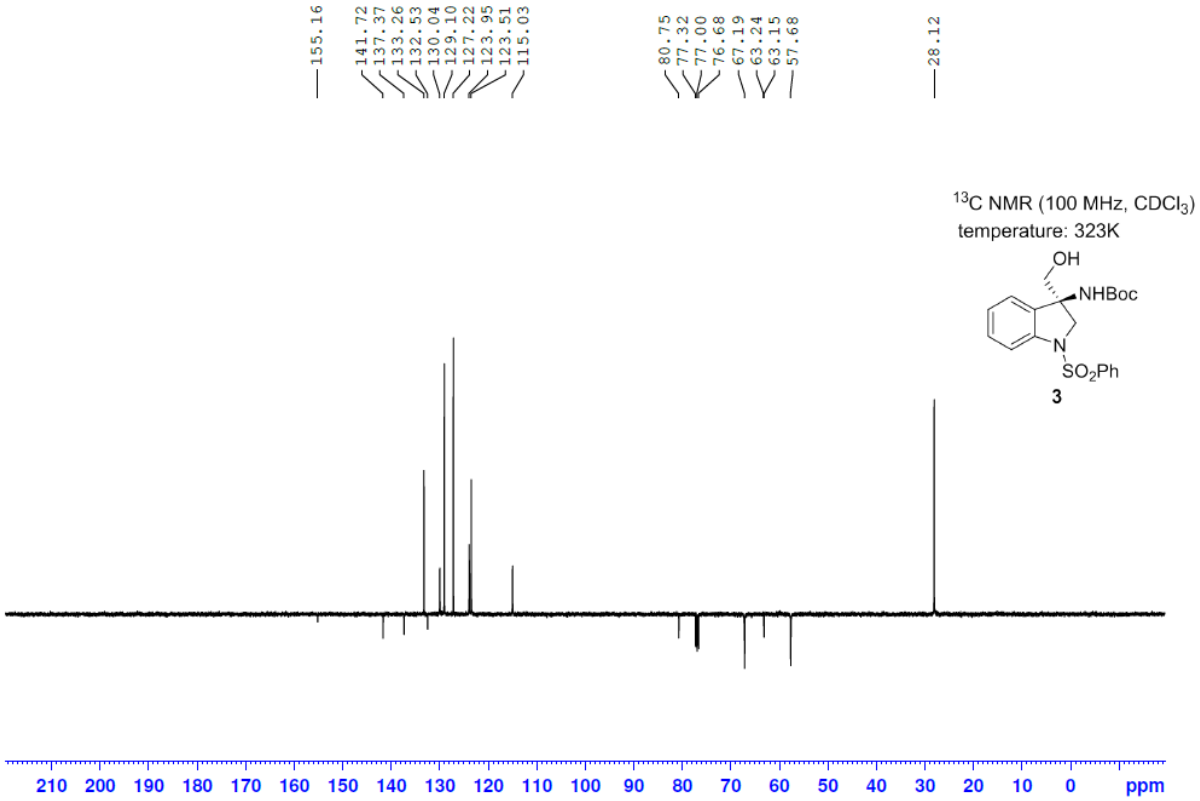


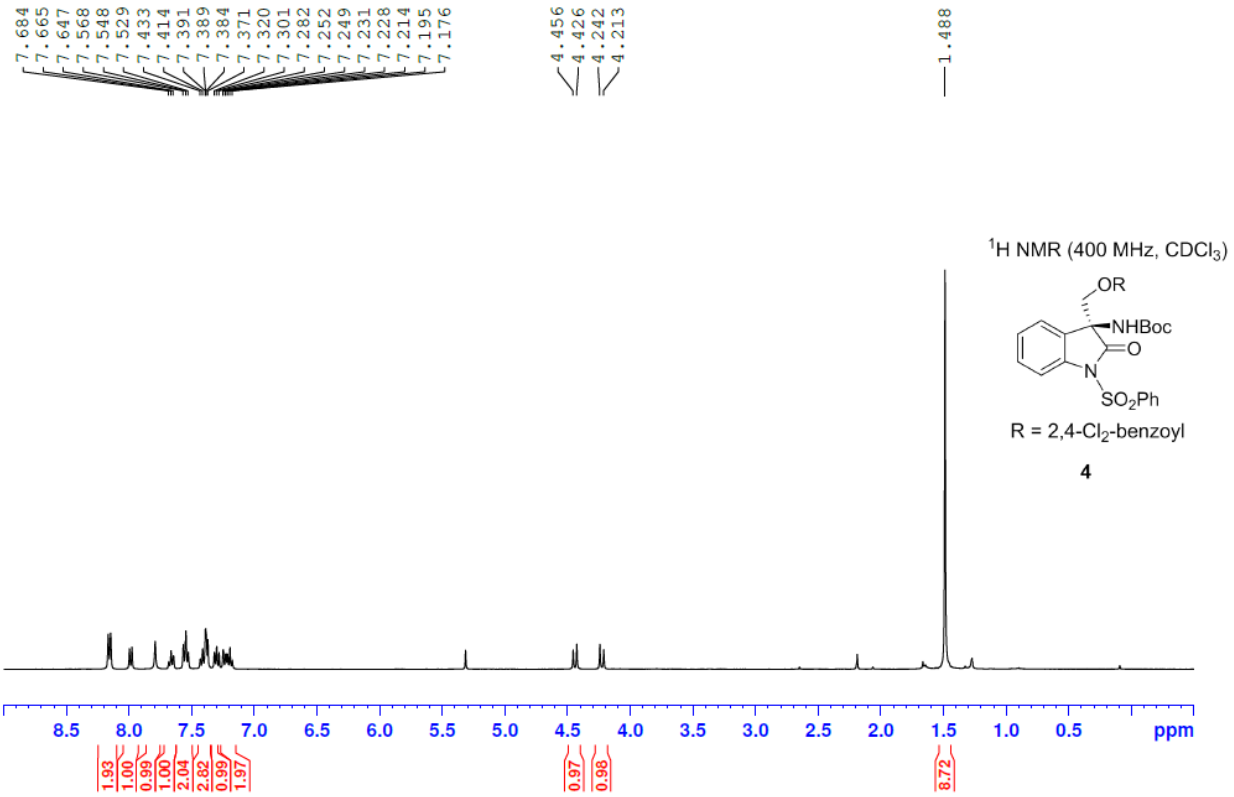
R = 2,4-Cl_2-benzoyl

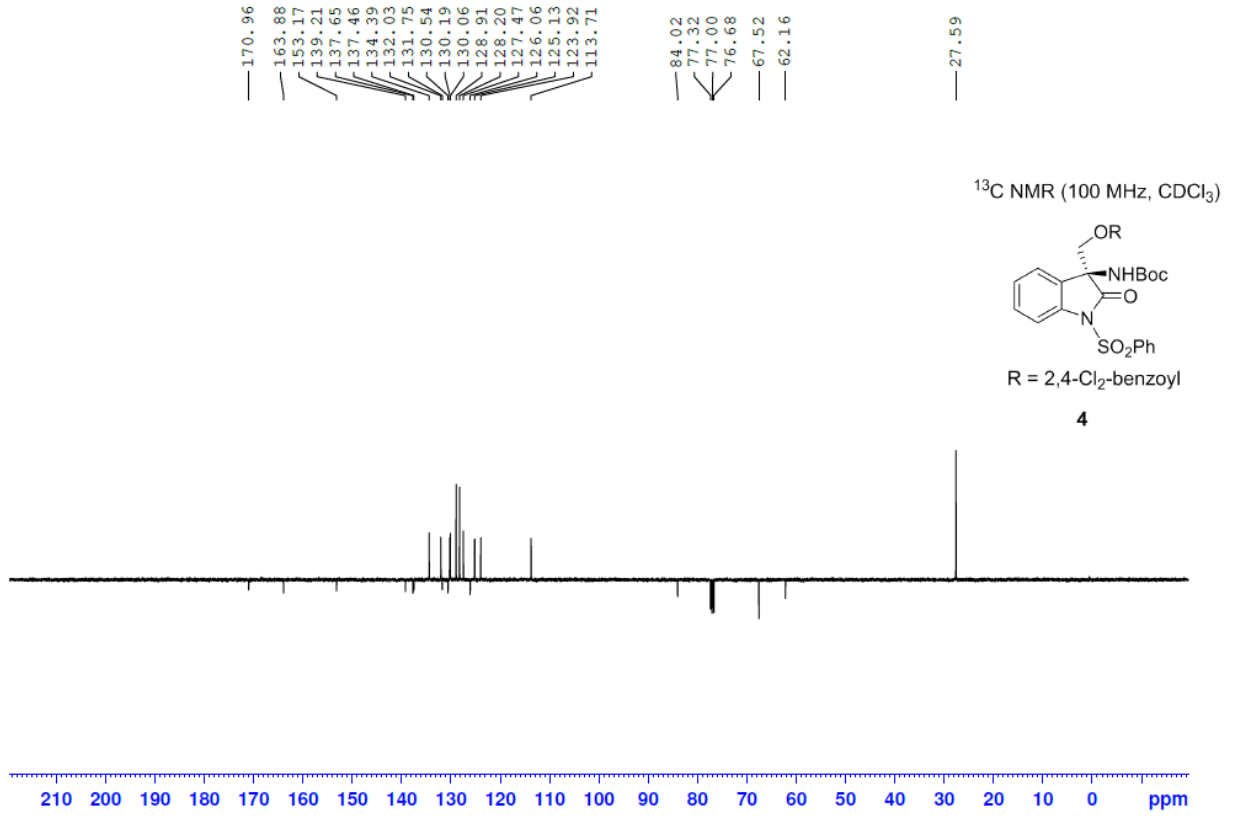
P9

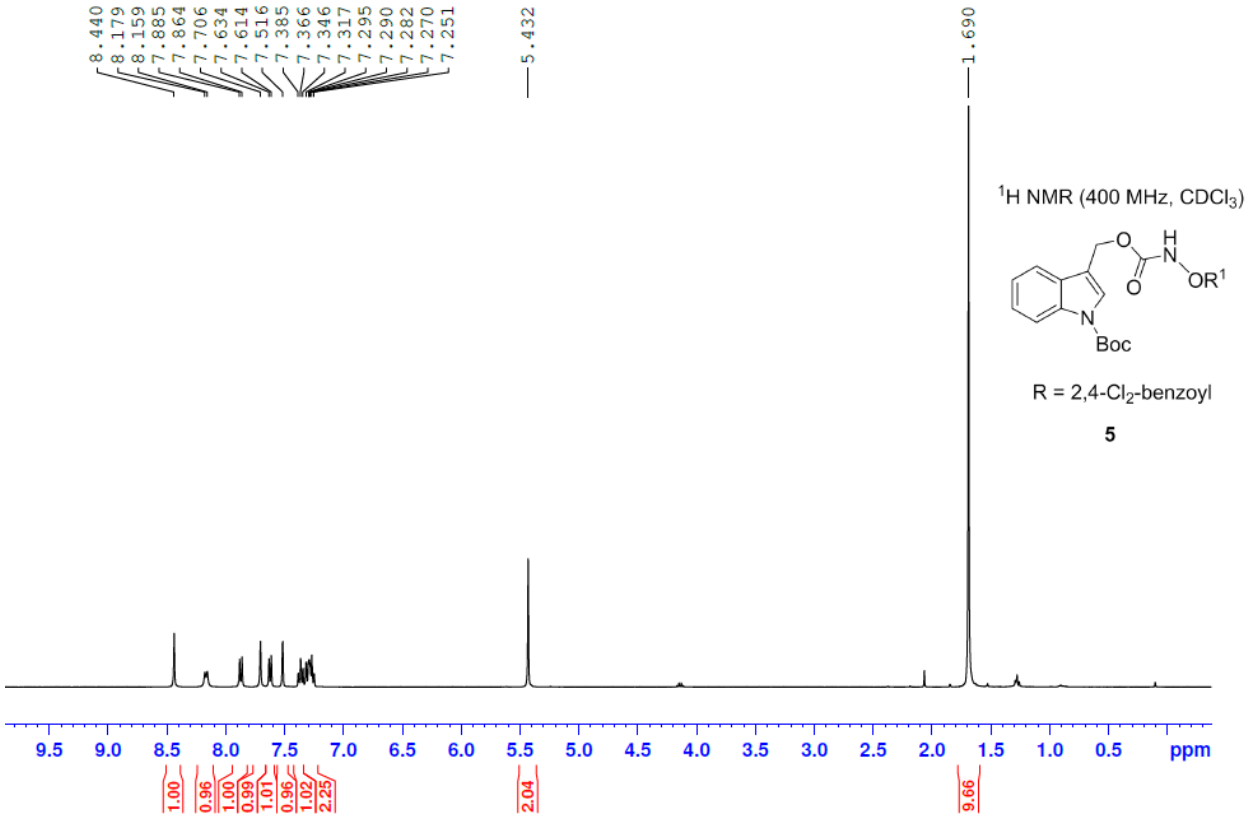



7.852
7.833
7.708
7.688
7.574
7.556
7.538
7.474
7.456
7.437
7.333
7.314
7.295
7.277
7.179
7.161
7.056
7.037
7.019
4.183
4.155
4.120
4.092
3.732
3.675
3.476
1.316
1H NMR (400 MHz, CDCl3)
temperature: 323 K
OH
NHBoc
N
SO2Ph
3
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.02
1.05
1.11
2.01
1.07
1.00
1.00
2.17
1.09
1.21
9.13


155.16
141.72
137.37
133.26
132.53
130.04
129.10
127.22
123.95
123.51
115.03
80.75
77.32
77.00
76.68
67.19
63.24
63.15
57.68
28.12
13C NMR (100 MHz, CDCl3)
temperature: 323K
OH
NHBoc
N
SO2Ph
3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


7.684
7.665
7.647
7.568
7.548
7.529
7.433
7.414
7.391
7.389
7.384
7.371
7.320
7.301
7.282
7.252
7.249
7.231
7.228
7.214
7.195
7.176
4.456
4.426
4.242
4.213
1.488
1H NMR (400 MHz, CDCl3)
OR
NHBoc
O
N
SO2Ph
R = 2,4-Cl2-benzoyl
4
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.93
1.00
0.99
1.00
2.04
2.82
0.99
1.97
0.97
0.98
8.72

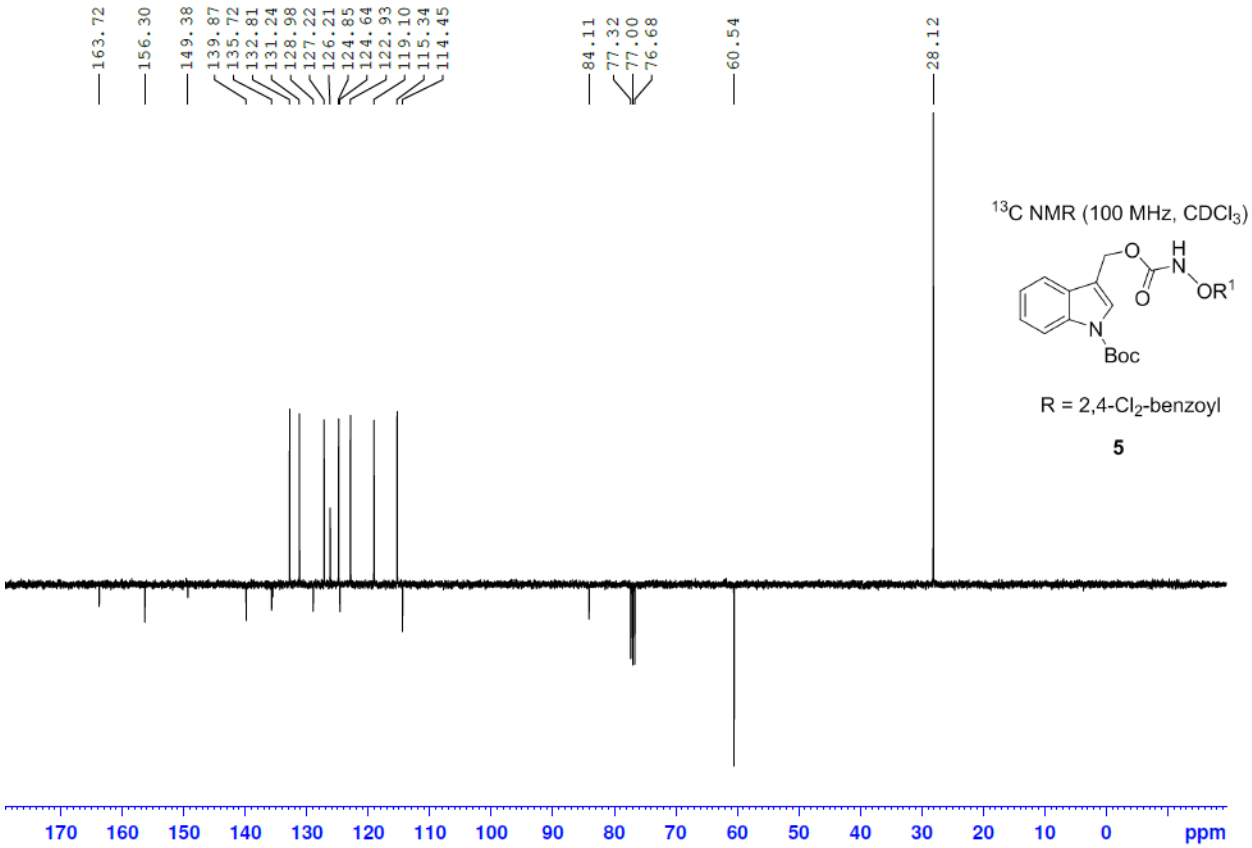

170.96
163.88
153.17
139.21
137.65
137.46
134.39
132.03
131.75
130.54
130.19
130.06
128.91
128.20
127.47
126.06
125.13
123.92
113.71
84.02
77.32
77.00
76.68
67.52
62.16
27.59
13C NMR (100 MHz, CDCl3)
OR
NHBoc
O
N
SO2Ph
R = 2,4-Cl2-benzoyl
4
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



^{1}H NMR (400 MHz, $CDCl_3$)

R = 2,4-Cl_2-benzoyl

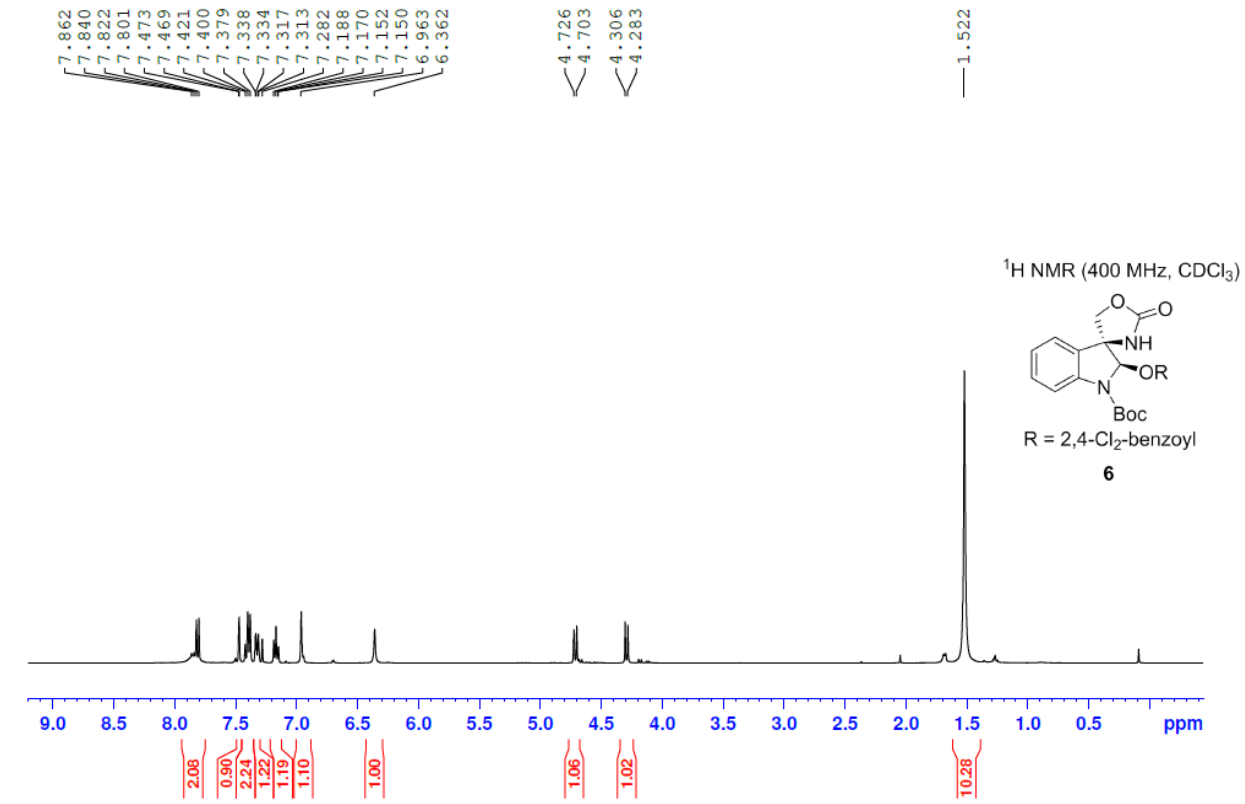
5

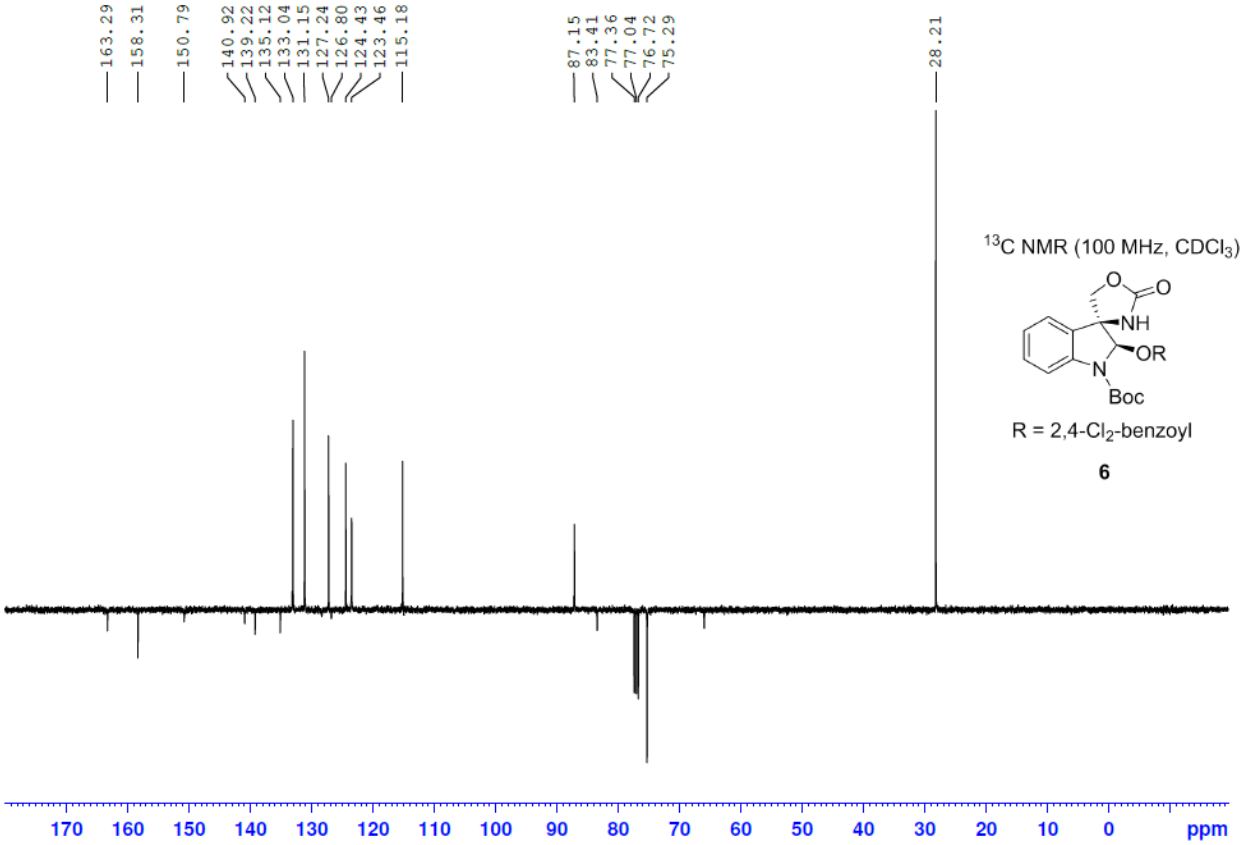


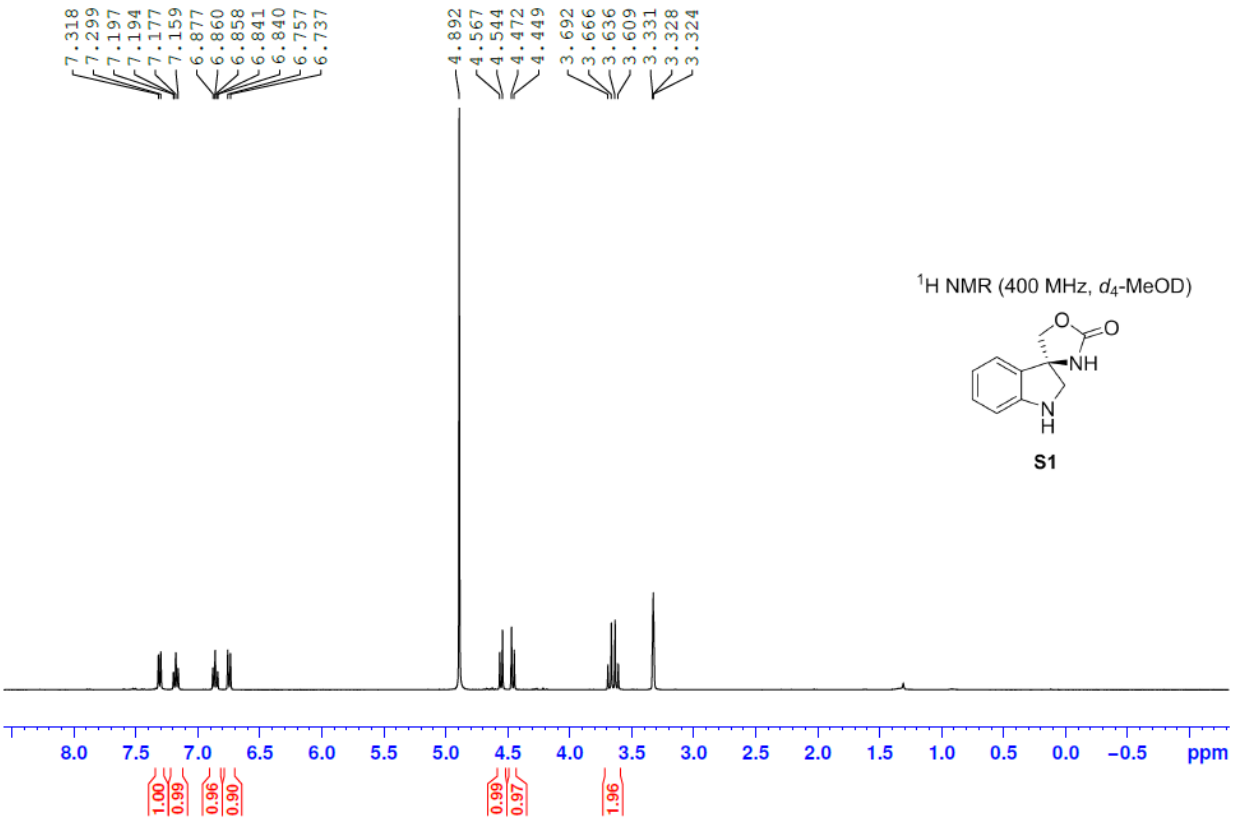
^{13}C NMR (100 MHz, $CDCl_3$)

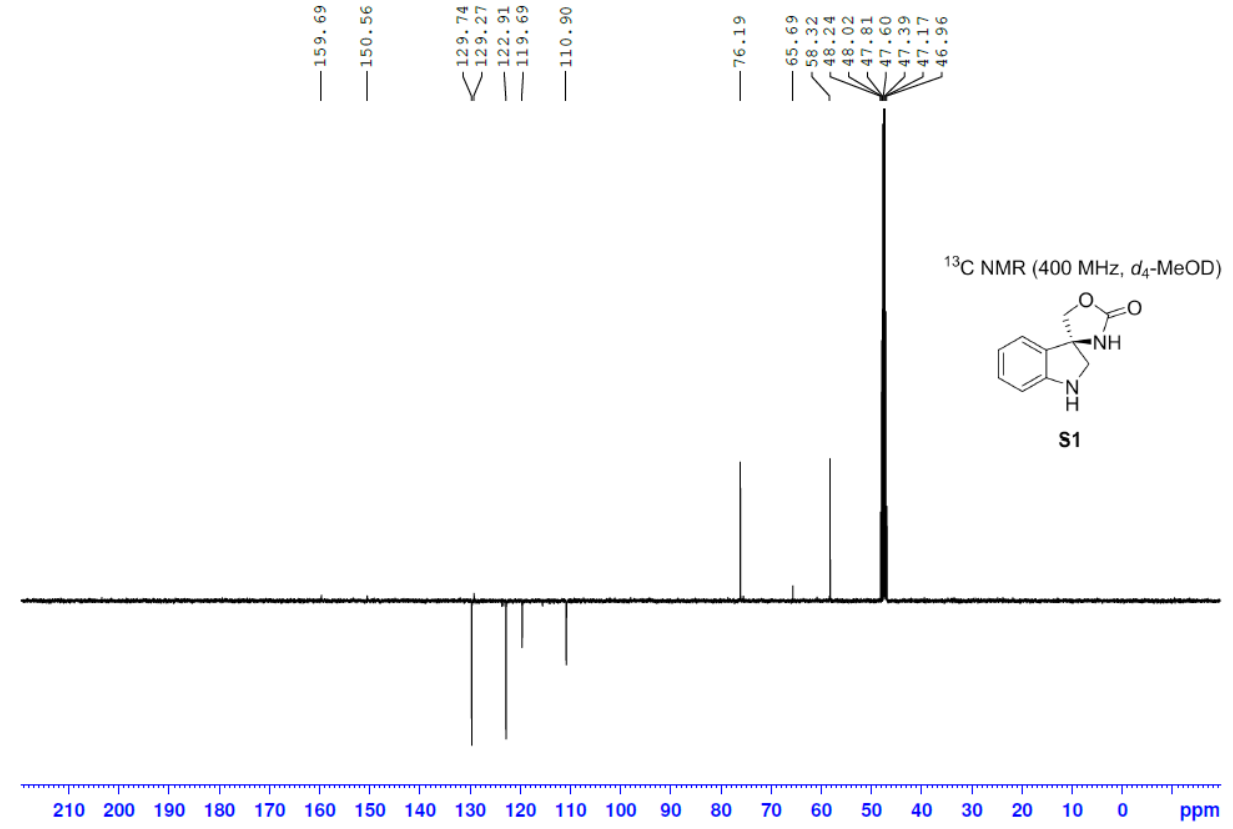
R = 2,4-Cl_2-benzoyl

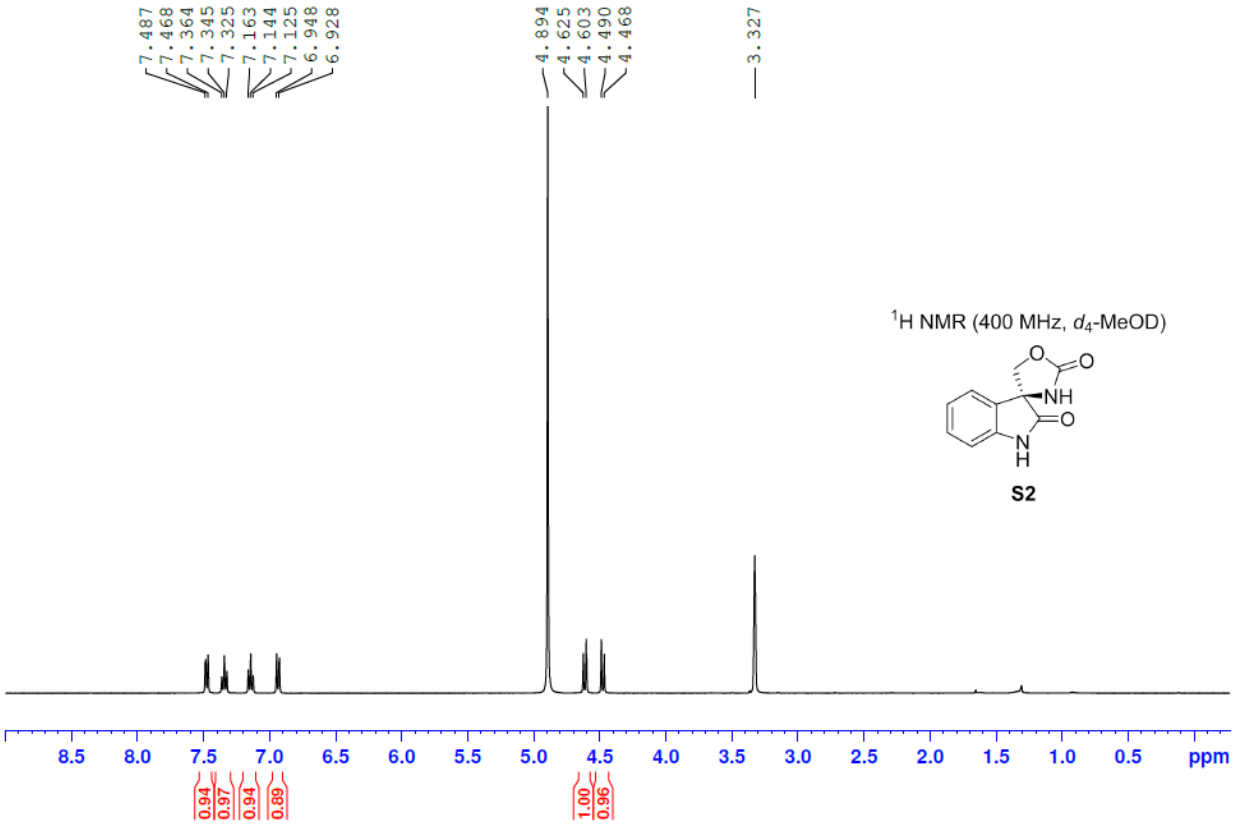
5

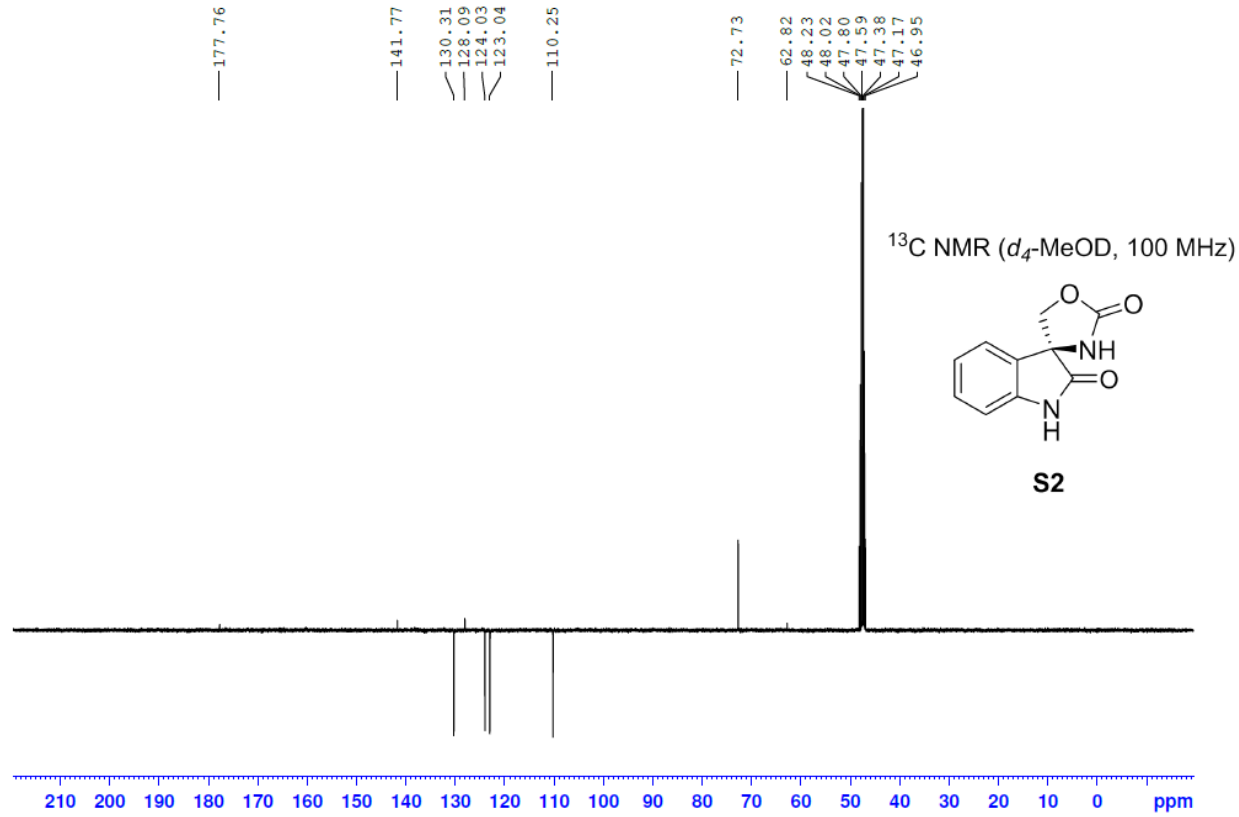

7.862
7.840
7.822
7.801
7.473
7.469
7.421
7.400
7.379
7.338
7.334
7.317
7.313
7.282
7.188
7.170
7.152
7.150
6.963
6.362
4.726
4.703
4.306
4.283
1.522
^{1}H NMR (400 MHz, CDCl$_3$)
O
O
NH
OR
N
Boc
R = 2,4-Cl$_2$-benzoyl
6
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.06
0.90
2.24
1.22
1.19
1.10
1.00
1.06
1.02
10.28

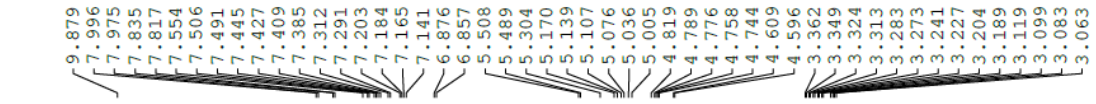

163.29
158.31
150.79
140.92
139.22
135.12
133.04
131.15
127.24
126.80
124.43
123.46
115.18
87.15
83.41
77.36
77.04
76.72
75.29
28.21
^{13}C NMR (100 MHz, CDCl$_3$)
O
O
NH
OR
N
Boc
R = 2,4-Cl$_2$-benzoyl
6
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


7.318
7.299
7.197
7.194
7.177
7.159
6.877
6.860
6.858
6.841
6.840
6.757
6.737
4.892
4.567
4.544
4.472
4.449
3.692
3.666
3.636
3.609
3.331
3.328
3.324
1H NMR (400 MHz, d4-MeOD)
O
O
NH
N
H
S1
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
−0.5
ppm
1.00
0.99
0.96
0.90
0.99
0.97
1.96

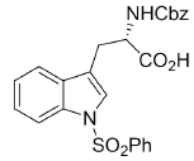

159.69
150.56
129.74
129.27
122.91
119.69
110.90
76.19
65.69
58.32
48.24
48.02
47.81
47.60
47.39
47.17
46.96
13C NMR (400 MHz, d4-MeOD)
O
O
NH
N
H
S1
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


7.487
7.468
7.364
7.345
7.325
7.163
7.144
7.125
6.948
6.928
4.894
4.625
4.603
4.490
4.468
3.327
^{1}H NMR (400 MHz, d_4-MeOD)
S2
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.94
0.97
0.94
0.69
1.00
0.96

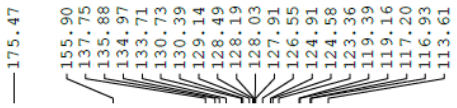

177.76
141.77
130.31
128.09
124.03
123.04
110.25
72.73
62.82
48.23
48.02
47.80
47.59
47.38
47.17
46.95
^{13}C NMR (d_4-MeOD, 100 MHz)
S2
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



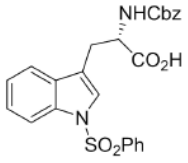
^{1}H NMR (400 MHz, $CDCl_3$)



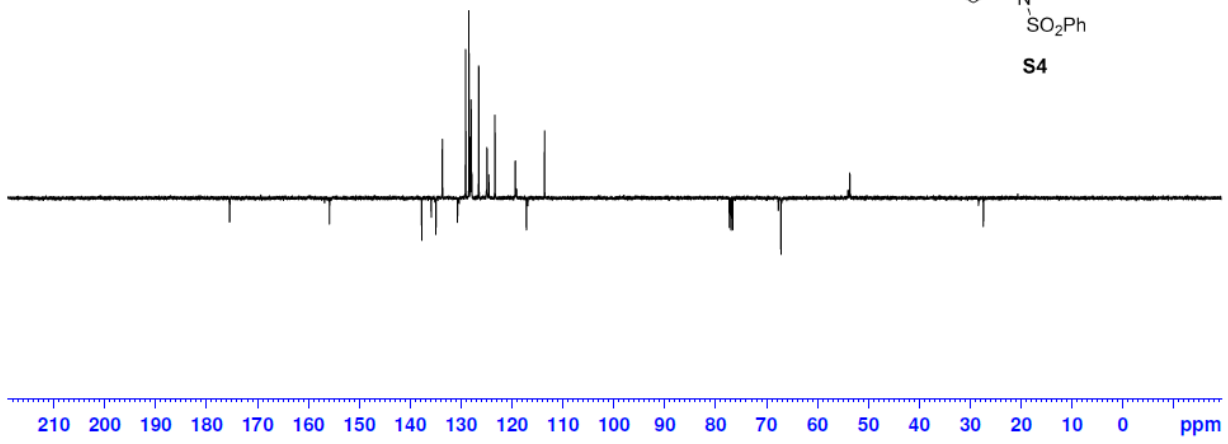
S4

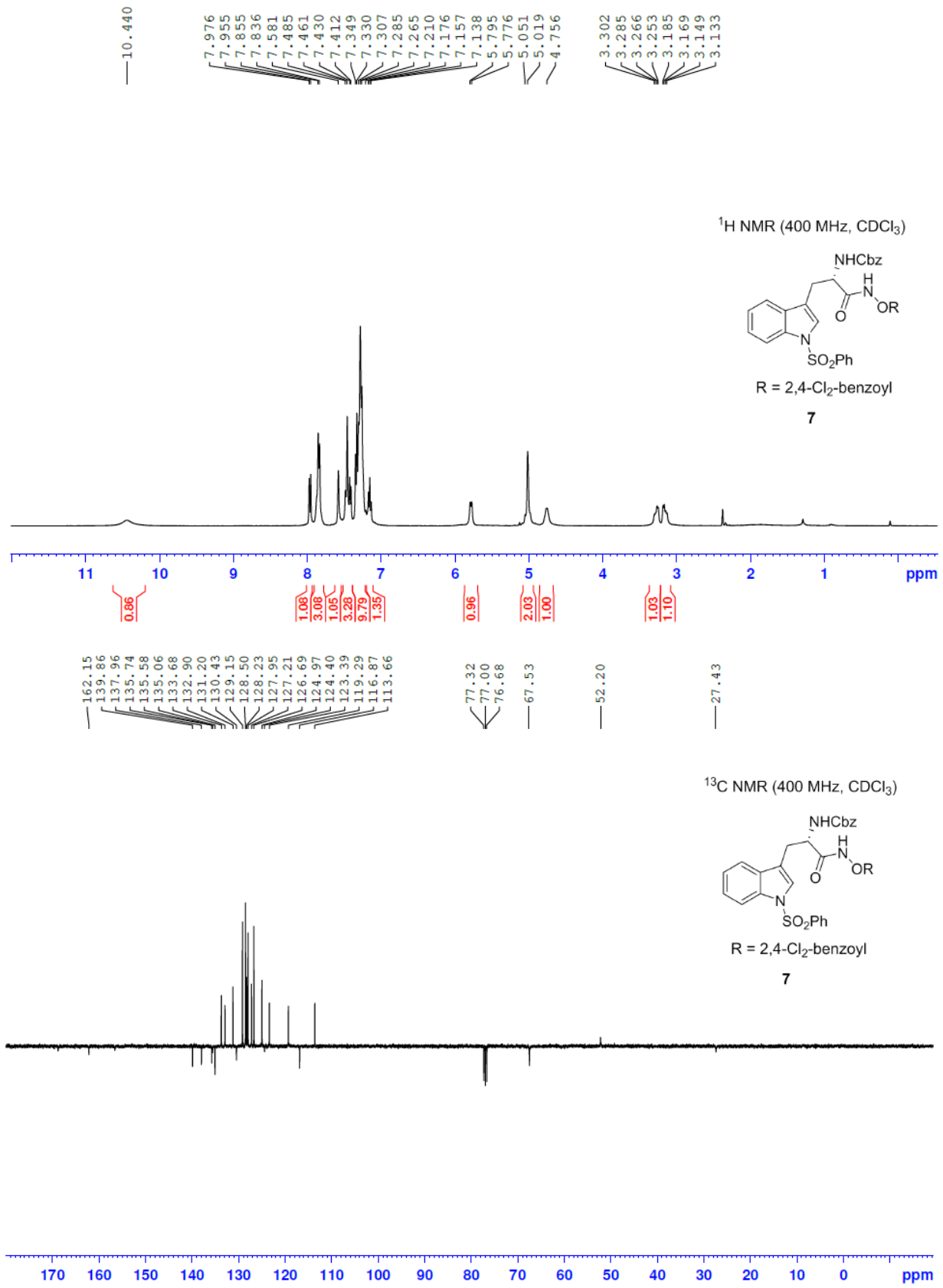


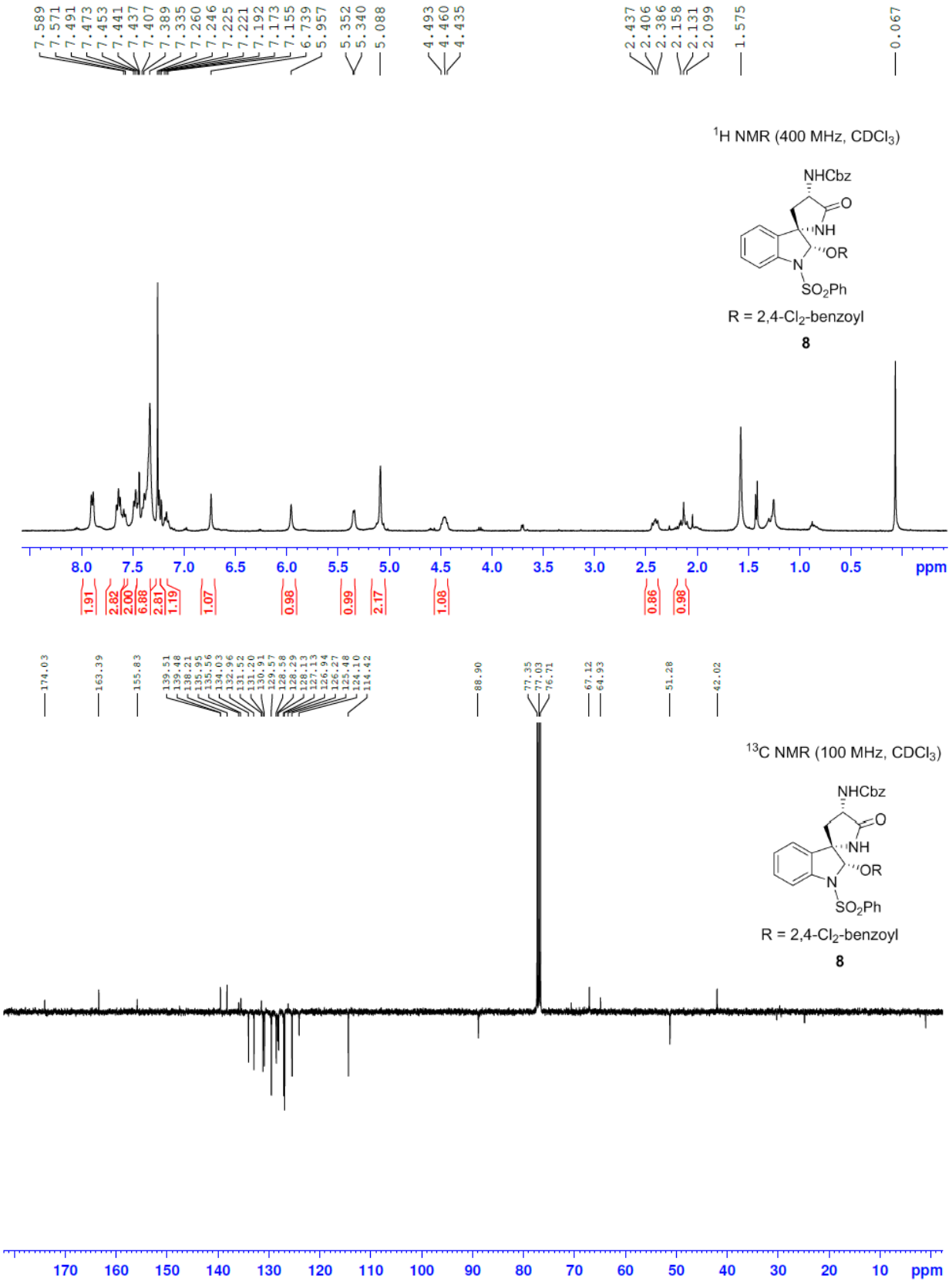
^{13}C NMR (400 MHz, $CDCl_3$)

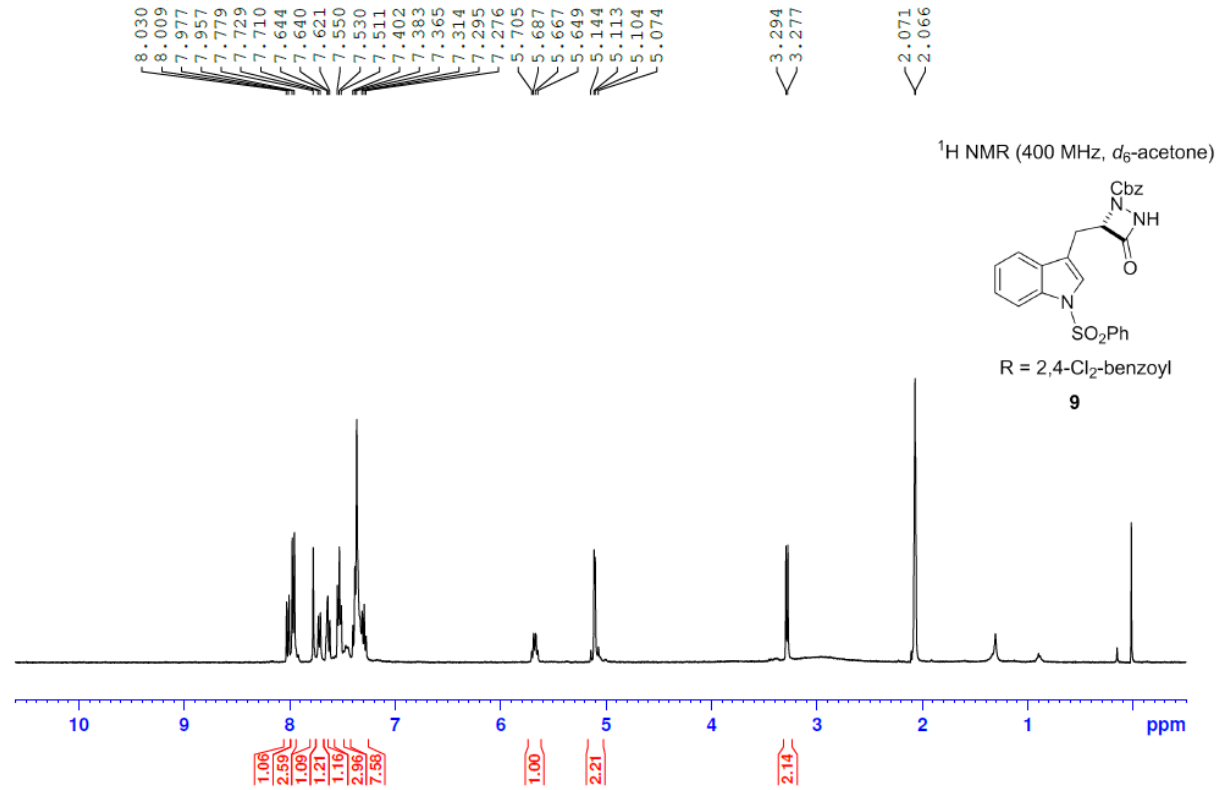


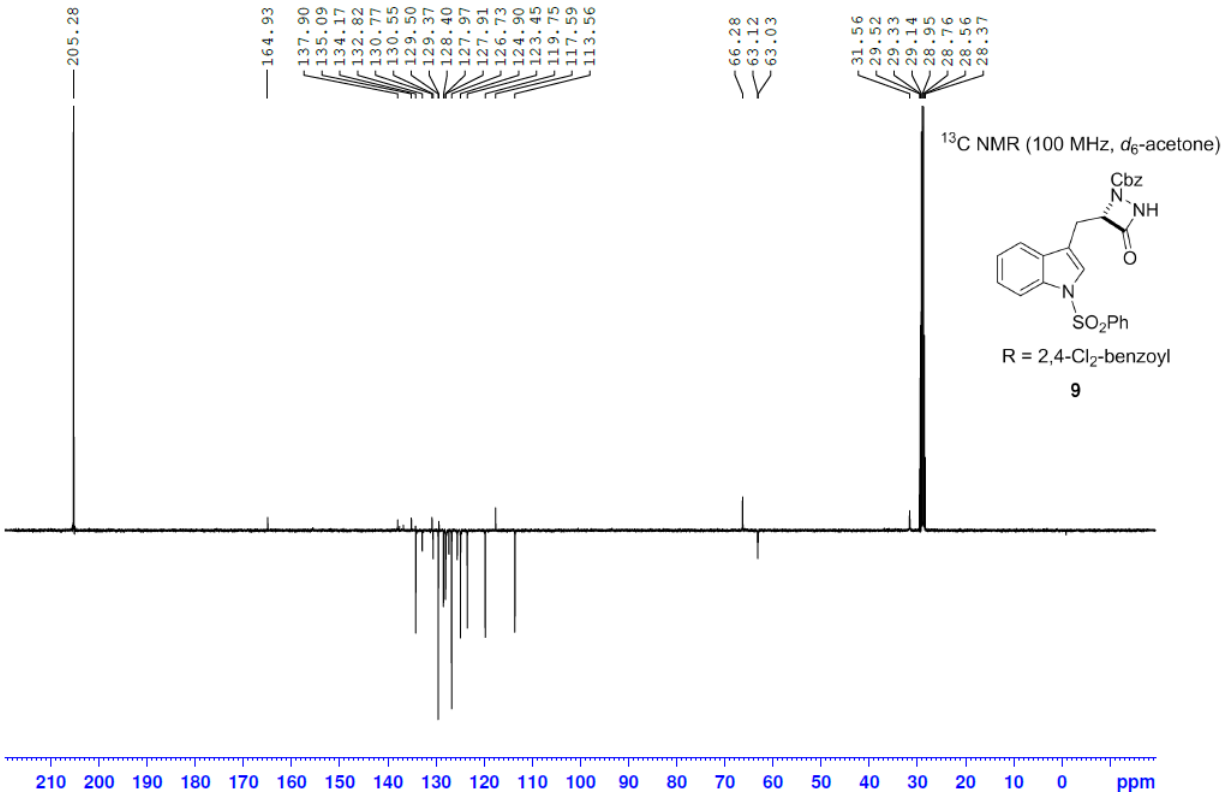
S4

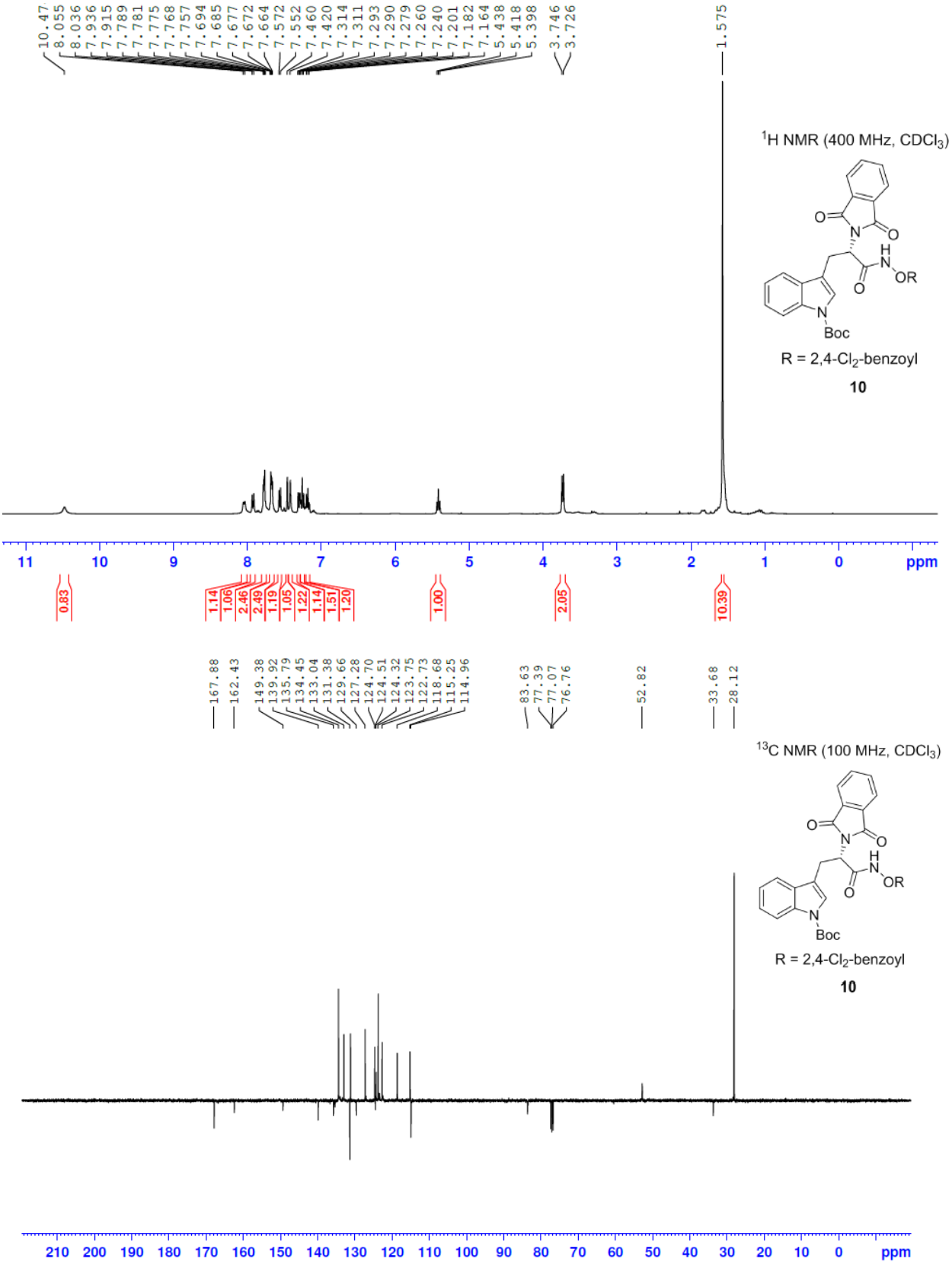


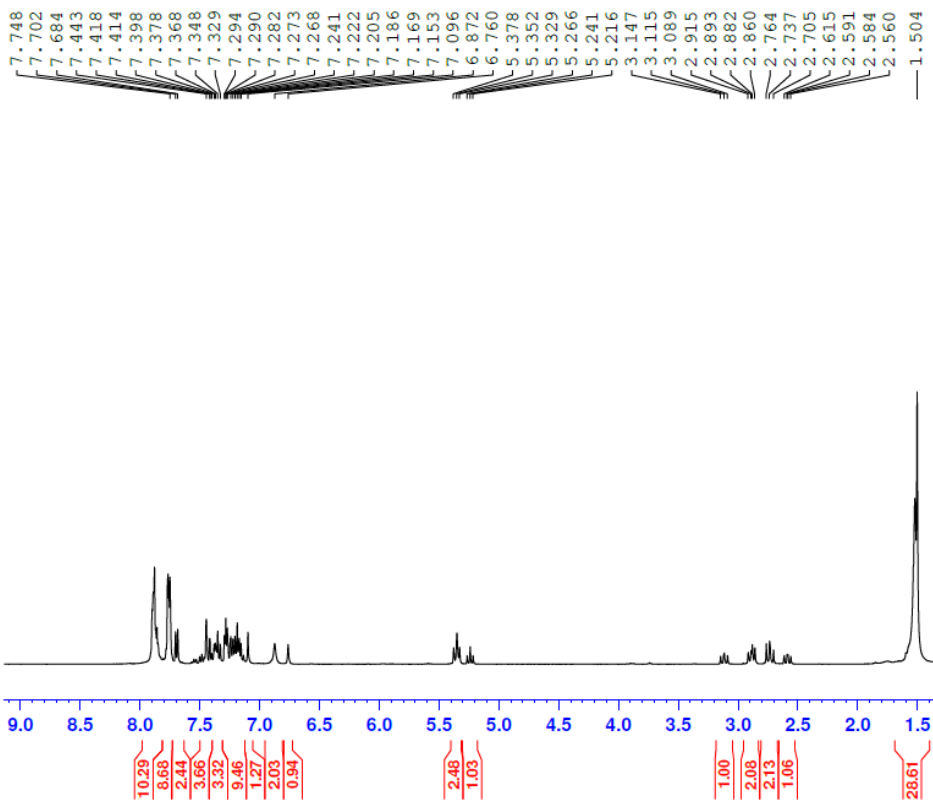

10.440
7.976
7.955
7.855
7.836
7.581
7.485
7.461
7.430
7.412
7.349
7.330
7.307
7.285
7.265
7.210
7.176
7.157
7.138
5.795
5.776
5.051
5.019
4.756
3.302
3.285
3.266
3.253
3.185
3.169
3.149
3.133
1H NMR (400 MHz, CDCl3)
NHCbz
H
N
OR
O
N
SO2Ph
R = 2,4-Cl2-benzoyl
7
11
10
9
8
7
6
5
4
3
2
1
ppm
0.86
1.08
3.08
1.05
3.28
9.79
1.35
0.96
2.03
1.00
1.03
1.10
162.15
139.86
137.96
135.74
135.58
135.06
133.68
132.90
131.20
130.43
129.15
128.50
128.23
127.95
127.21
126.69
124.97
124.40
123.39
119.29
116.87
113.66
77.32
77.00
76.68
67.53
52.20
27.43
13C NMR (400 MHz, CDCl3)
NHCbz
H
N
OR
O
N
SO2Ph
R = 2,4-Cl2-benzoyl
7
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


7.589
7.571
7.491
7.473
7.453
7.441
7.437
7.407
7.389
7.335
7.260
7.246
7.225
7.221
7.192
7.173
7.155
6.739
5.957
5.352
5.340
5.088
4.493
4.460
4.435
2.437
2.406
2.386
2.158
2.131
2.099
1.575
0.067
1H NMR (400 MHz, CDCl3)
NHCbz
O
NH
OR
N
SO2Ph
R = 2,4-Cl2-benzoyl
8
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.91
2.82
2.00
6.88
2.81
1.19
1.07
0.98
0.99
2.17
1.08
0.86
0.98
174.03
163.39
155.83
139.51
139.48
138.21
135.55
135.56
134.03
132.96
131.52
131.20
130.91
129.57
128.58
128.29
128.13
127.13
126.94
126.27
125.48
124.10
114.42
88.90
77.35
77.03
76.71
67.12
64.93
51.28
42.02
13C NMR (100 MHz, CDCl3)
NHCbz
O
NH
OR
N
SO2Ph
R = 2,4-Cl2-benzoyl
8
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

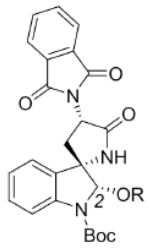

8.030
8.009
7.977
7.957
7.779
7.729
7.710
7.644
7.640
7.621
7.550
7.530
7.511
7.402
7.383
7.365
7.314
7.295
7.276
5.705
5.687
5.667
5.649
5.144
5.113
5.104
5.074
3.294
3.277
2.071
2.066
1H NMR (400 MHz, d6-acetone)
Cbz
NH
O
N
SO2Ph
R = 2,4-Cl2-benzoyl
9
10
9
8
7
6
5
4
3
2
1
ppm
1.06
2.59
1.08
1.21
1.16
2.96
7.58
1.00
2.21
2.14


205.28
164.93
137.90
135.09
134.17
132.82
130.77
130.55
129.50
129.37
128.40
127.97
127.91
126.73
124.90
123.45
119.75
117.59
113.56
66.28
63.12
63.03
31.56
29.52
29.33
29.14
28.95
28.76
28.56
28.37
13C NMR (100 MHz, d6-acetone)
Cbz
NH
O
N
SO2Ph
R = 2,4-Cl2-benzoyl
9
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

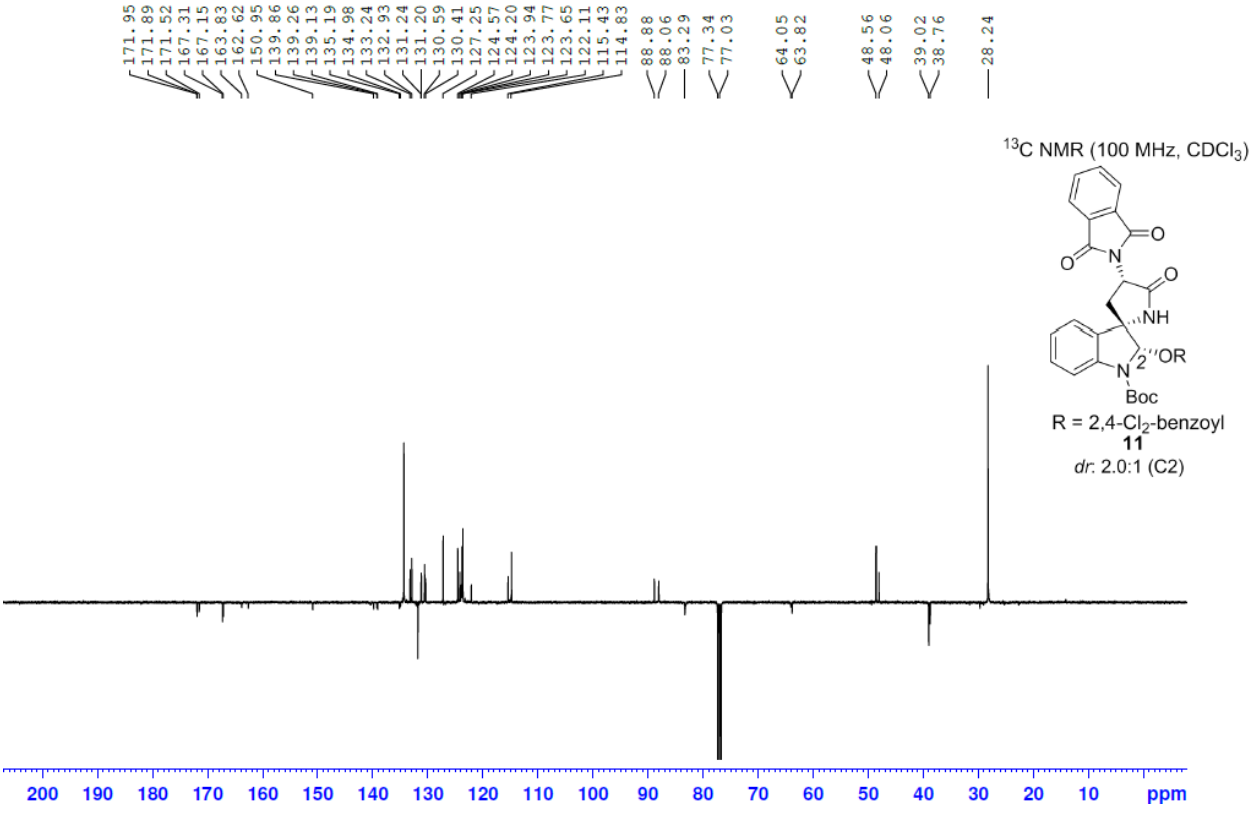

10.47
8.055
8.036
7.936
7.915
7.789
7.781
7.775
7.768
7.757
7.694
7.685
7.677
7.672
7.664
7.572
7.552
7.460
7.420
7.314
7.311
7.293
7.290
7.279
7.260
7.240
7.201
7.182
7.164
5.438
5.418
5.398
3.746
3.726
1.575
^{1}H NMR (400 MHz, CDCl$_3$)
R = 2,4-Cl$_2$-benzoyl
10
11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.83 1.14 1.06 2.46 2.49 1.19 1.05 1.22 1.14 1.51 1.20 1.00 2.05 10.39
167.88
162.43
149.38
139.92
135.79
134.45
133.04
131.38
129.66
127.28
124.70
124.51
124.32
123.75
122.73
118.68
115.25
114.96
83.63
77.39
77.07
76.76
52.82
33.68
28.12
^{13}C NMR (100 MHz, CDCl$_3$)
R = 2,4-Cl$_2$-benzoyl
10
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



^{1}H NMR (400 MHz, $CDCl_3$)



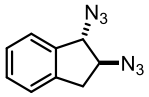
R = 2,4-Cl_2-benzoyl
11
dr: 2.0:1 (C2)



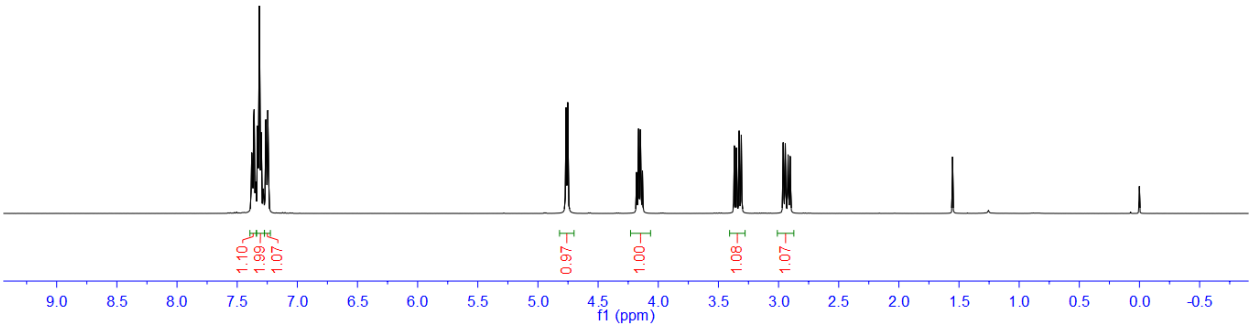
^{13}C NMR (100 MHz, $CDCl_3$)

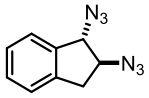
R = 2,4-Cl_2-benzoyl
11
dr: 2.0:1 (C2)

Appendix D ^{1}H and ^{13}C Spectra of Compounds in Chapter IV

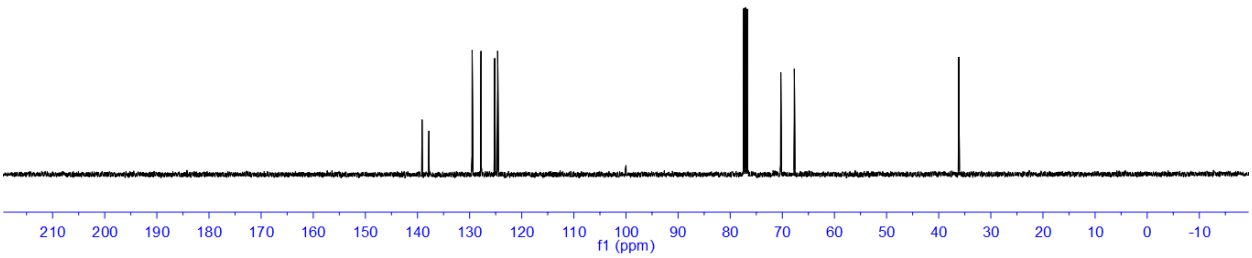


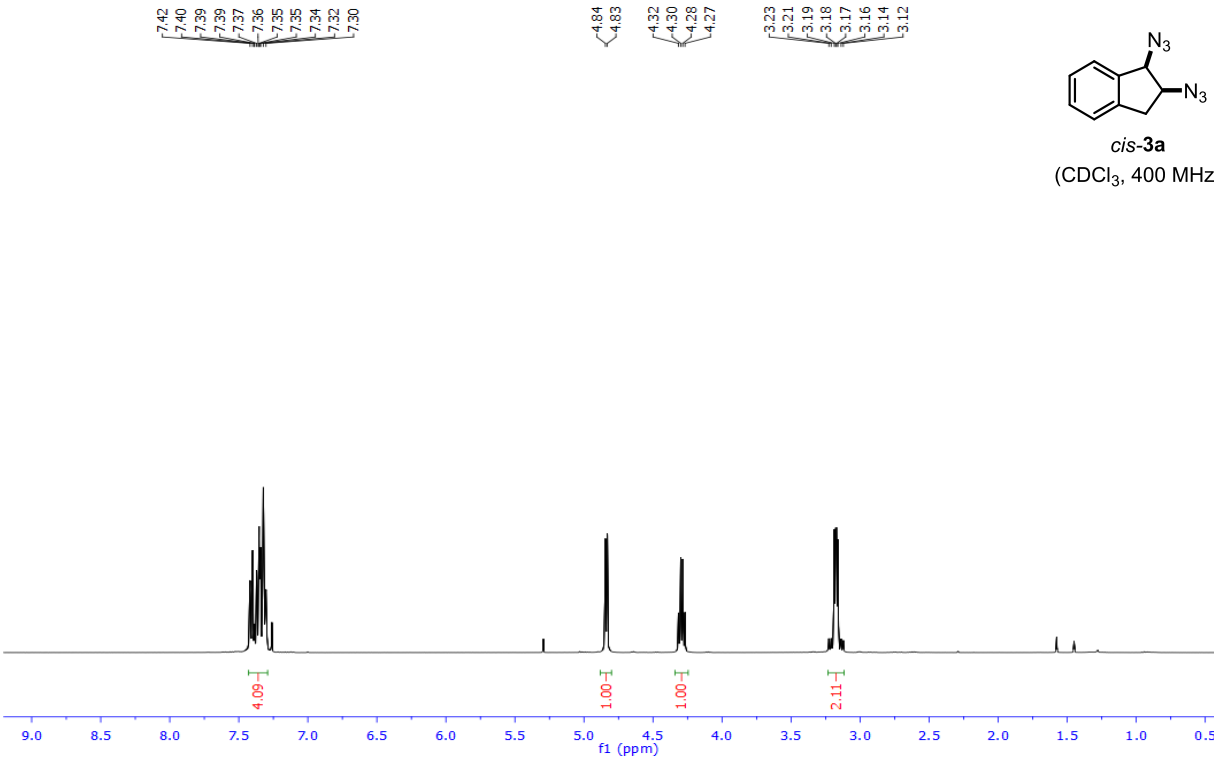
trans-**3a**
($CDCl_3$, 400 MHz)



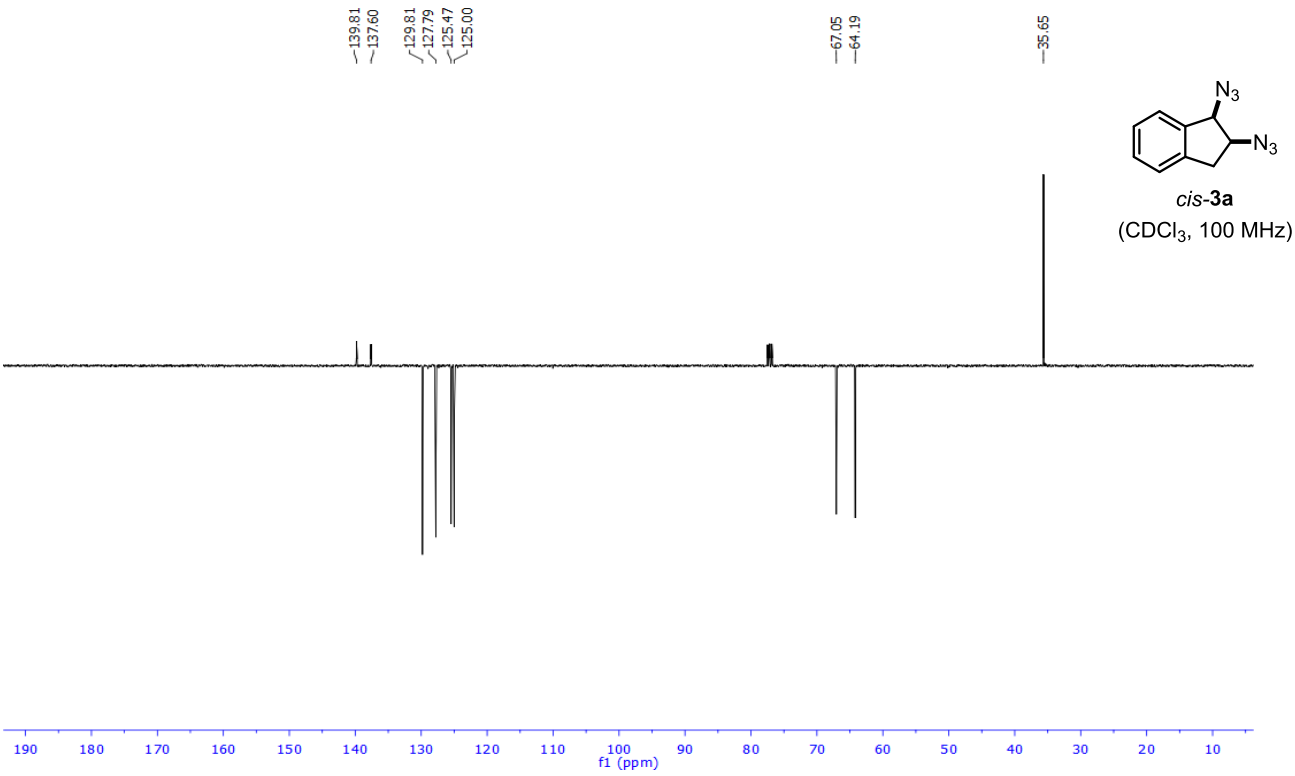


trans-**3a**
($CDCl_3$, 100 MHz)

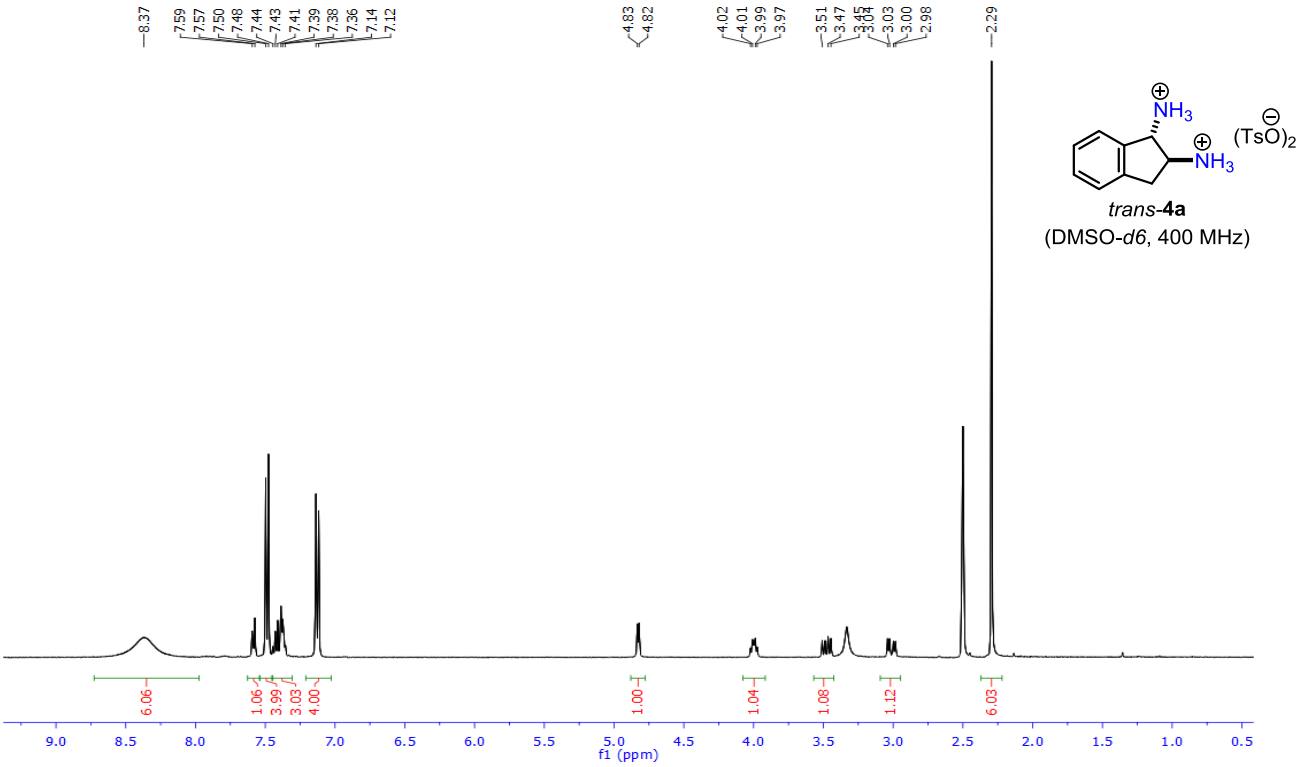


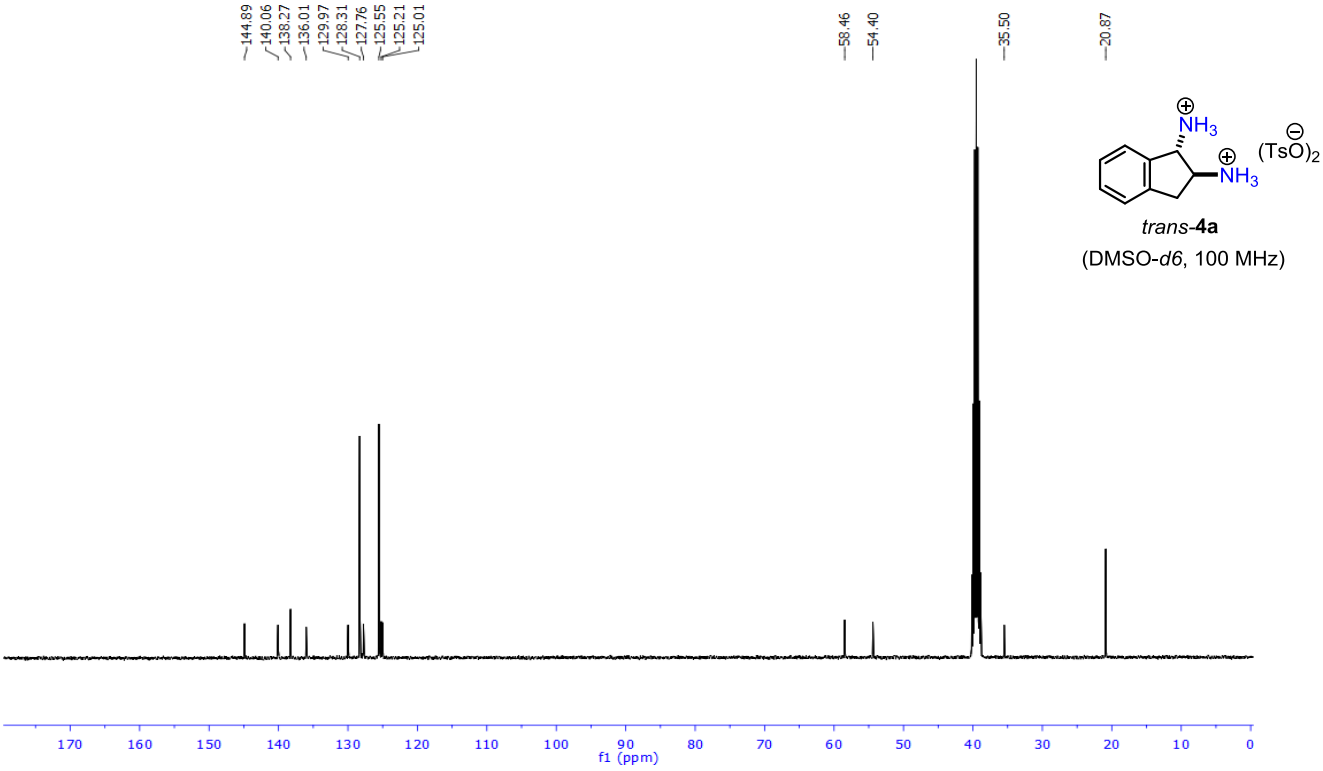


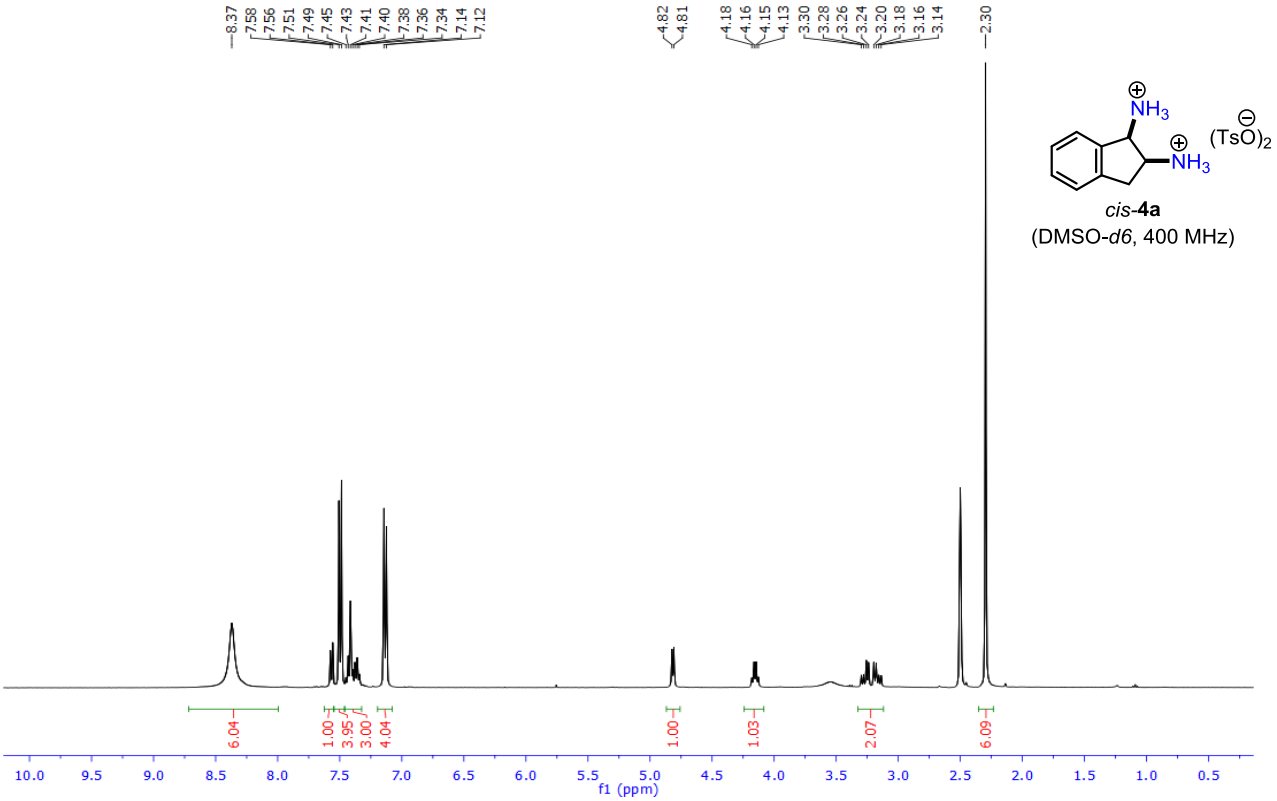
cis-**3a**
($CDCl_3$, 400 MHz)



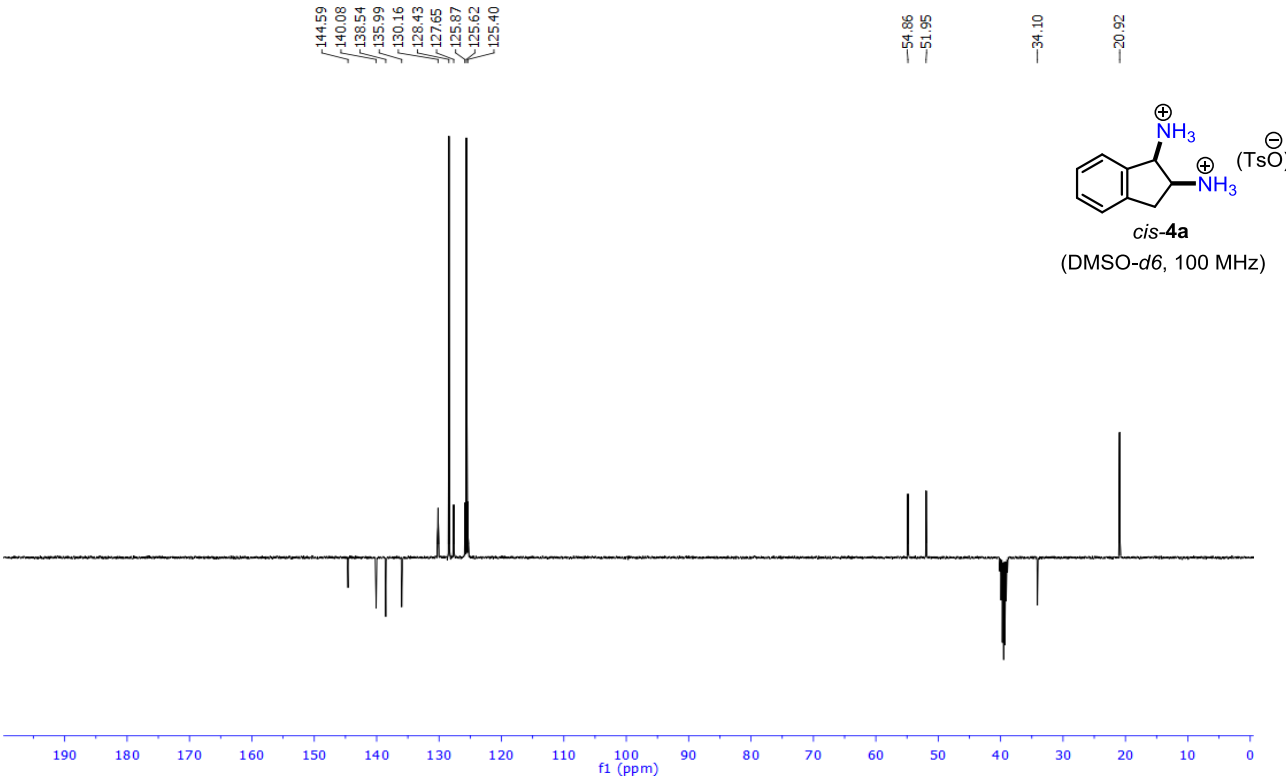
cis-**3a**
($CDCl_3$, 100 MHz)


8.37
7.59
7.57
7.50
7.48
7.44
7.43
7.41
7.39
7.38
7.36
7.14
7.12
4.83
4.82
4.02
4.01
3.99
3.97
3.51
3.47
3.45
3.04
3.03
3.00
2.98
2.29
6.06
1.06
3.99
3.03
4.00
1.00
1.04
1.08
1.12
6.03
f1 (ppm)
NH3
NH3
(TsO)2
trans-4a
(DMSO-d6, 400 MHz)

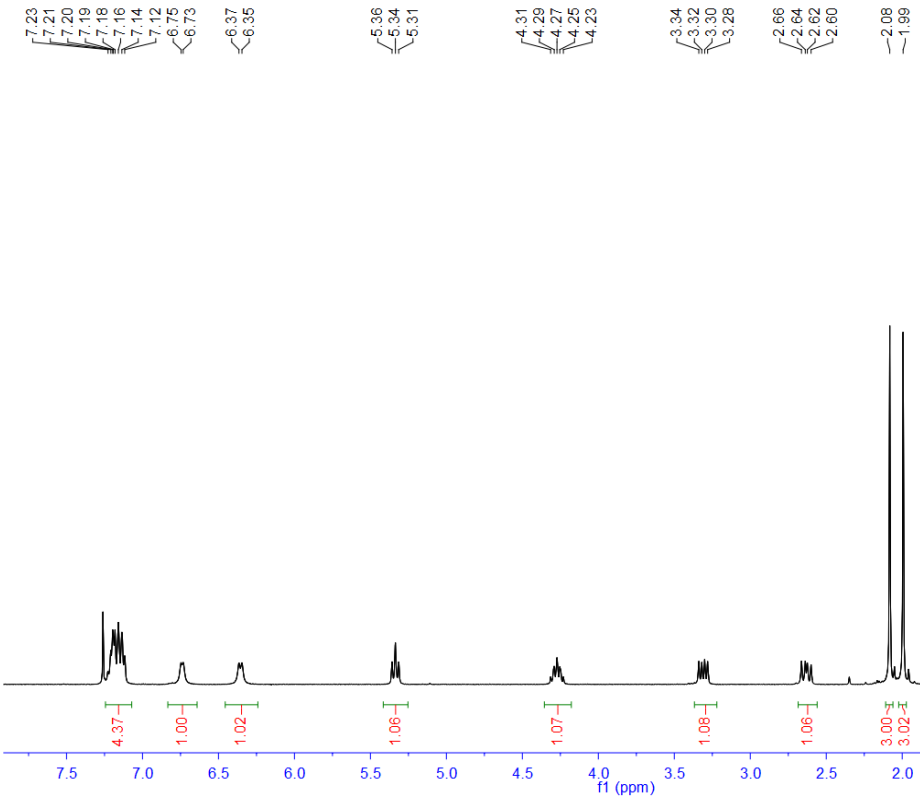

144.89
140.06
138.27
136.01
129.97
128.31
127.76
125.55
125.21
125.01
58.46
54.40
35.50
20.87
f1 (ppm)
NH3
NH3
(TsO)2
trans-4a
(DMSO-d6, 100 MHz)

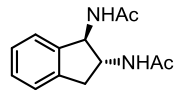


cis-**4a**
(DMSO-*d6*, 400 MHz)



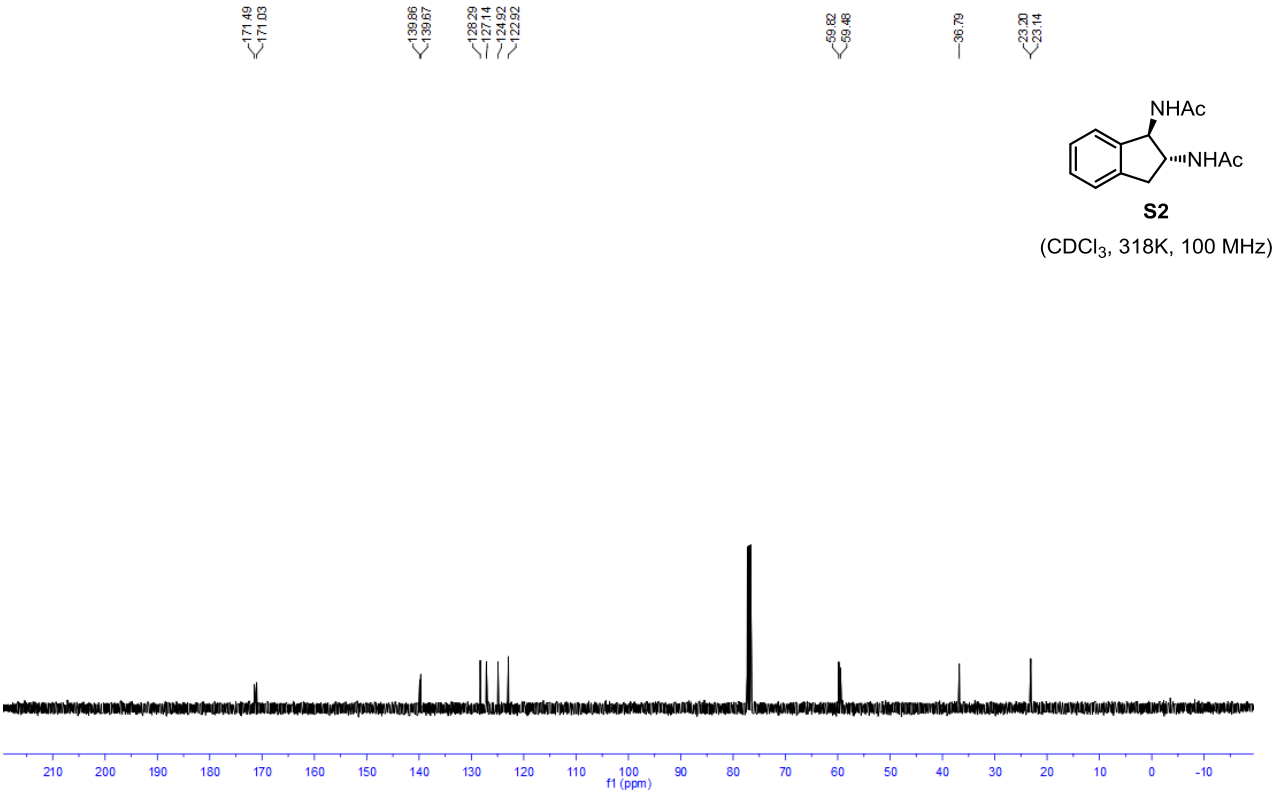
cis-**4a**
(DMSO-*d6*, 100 MHz)





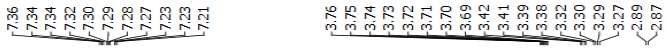
S2

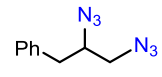
($CDCl_3$, 318K, 400 MHz)



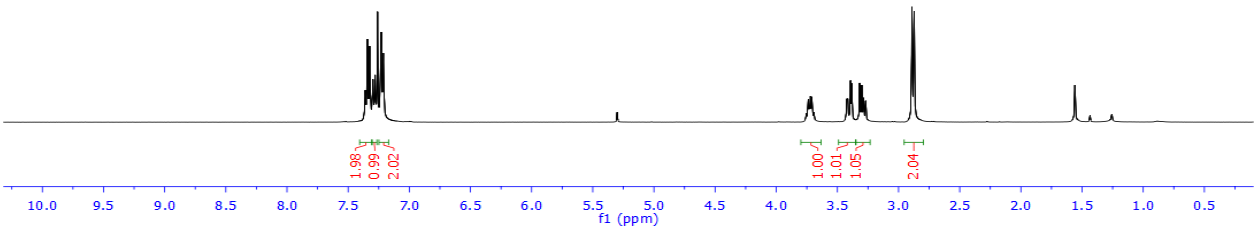
S2

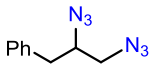
($CDCl_3$, 318K, 100 MHz)



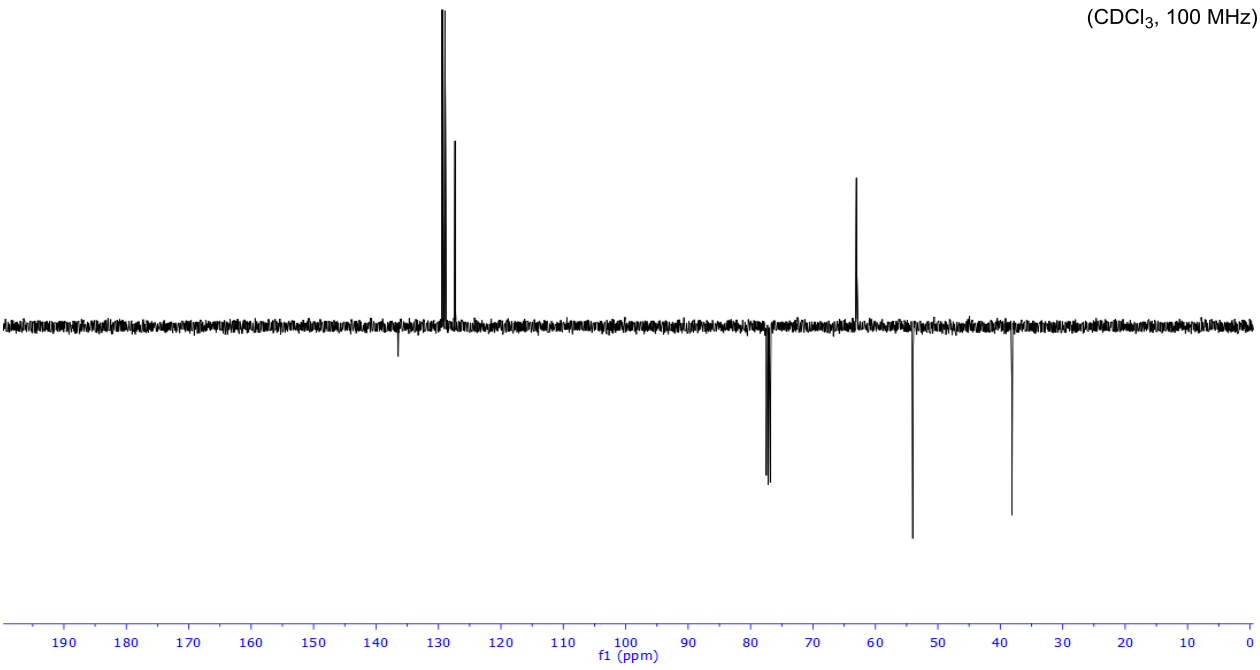


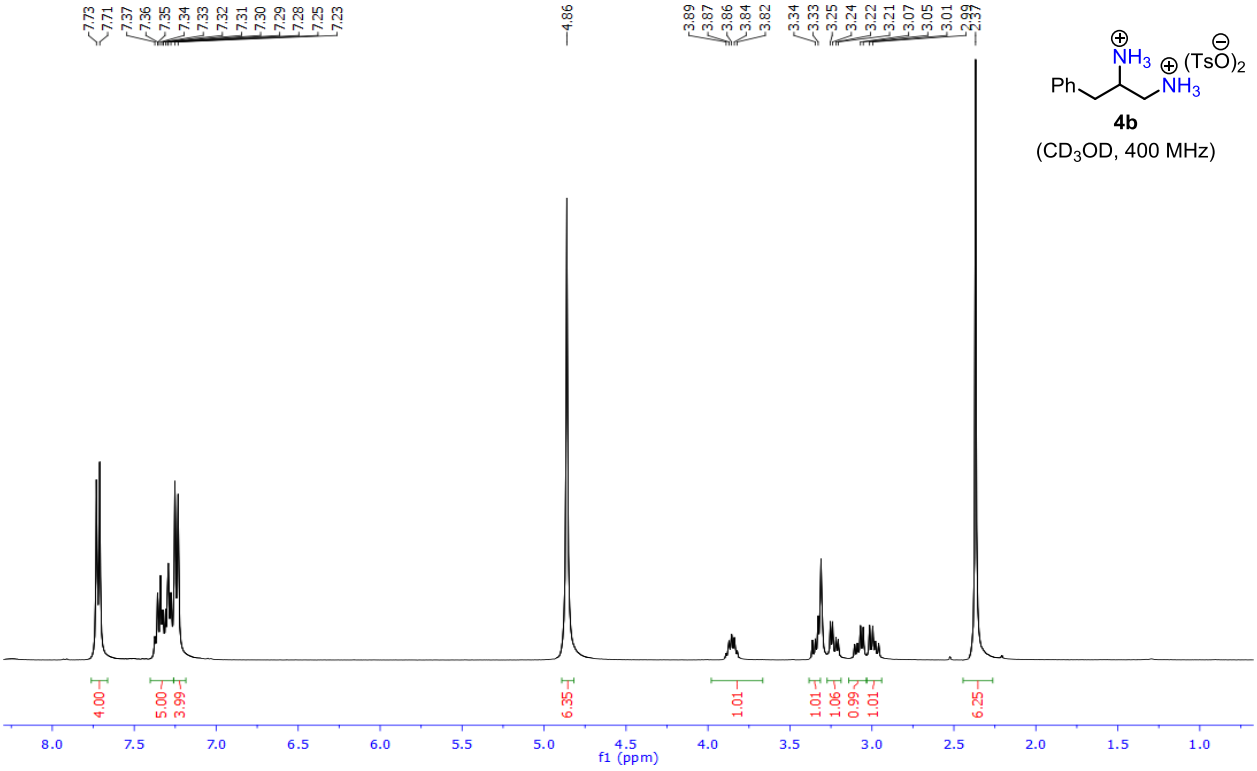
3b
($CDCl_3$, 400 MHz)

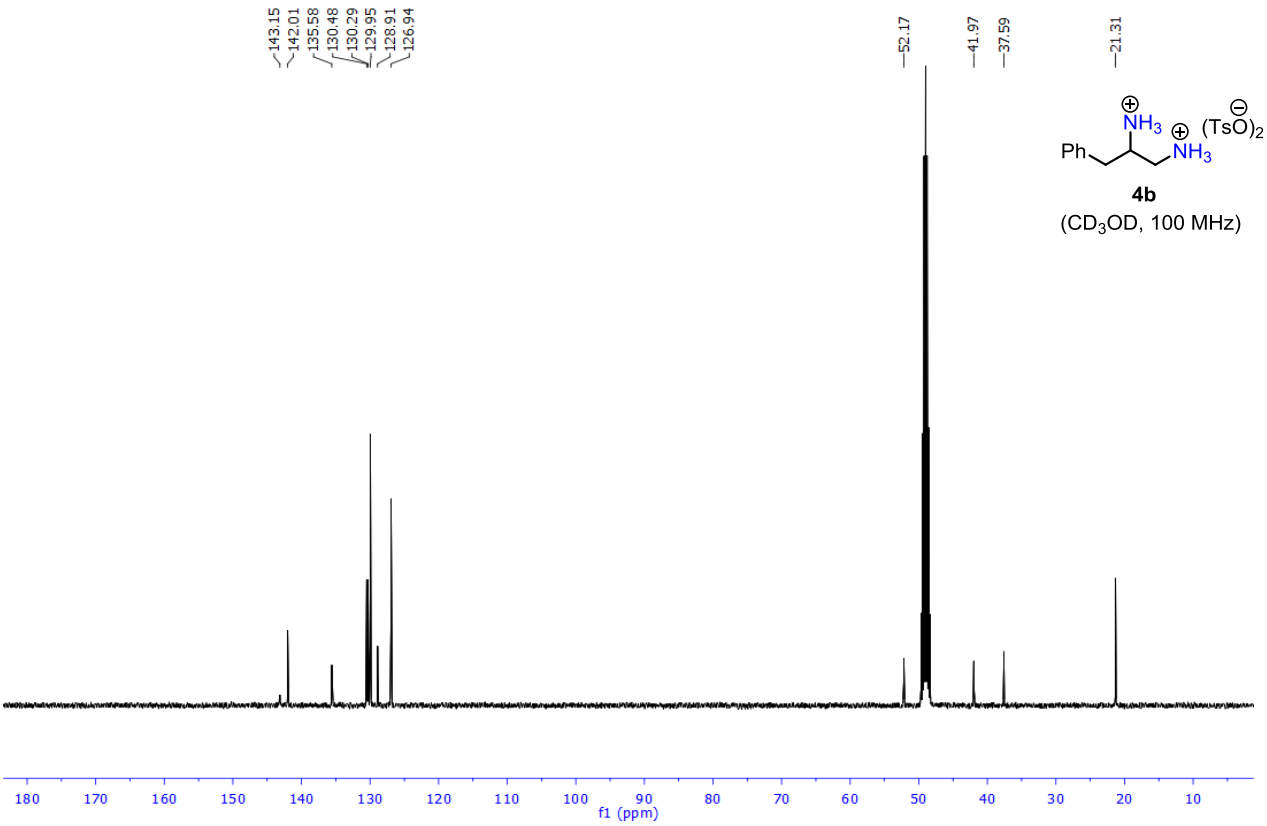




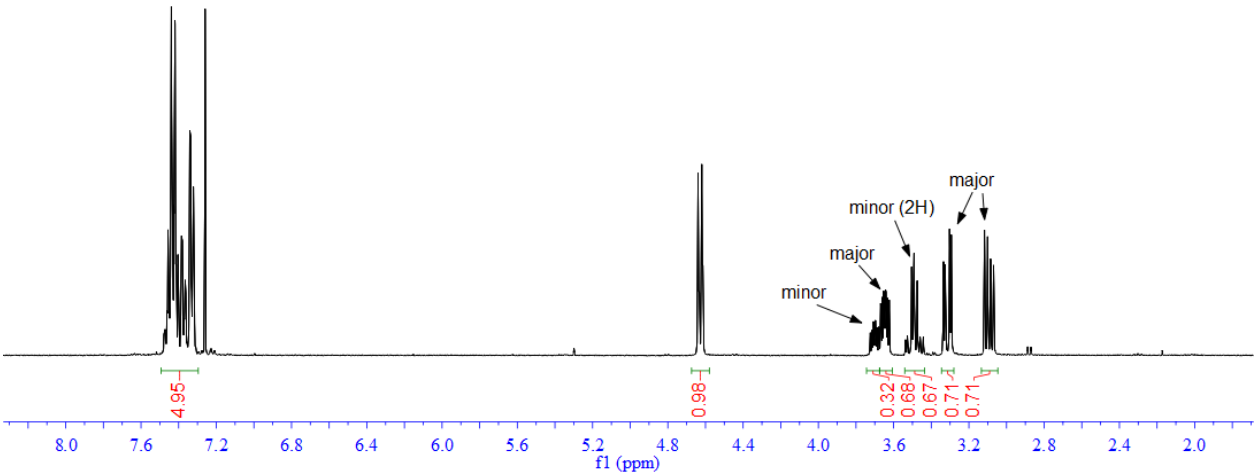
3b
($CDCl_3$, 100 MHz)



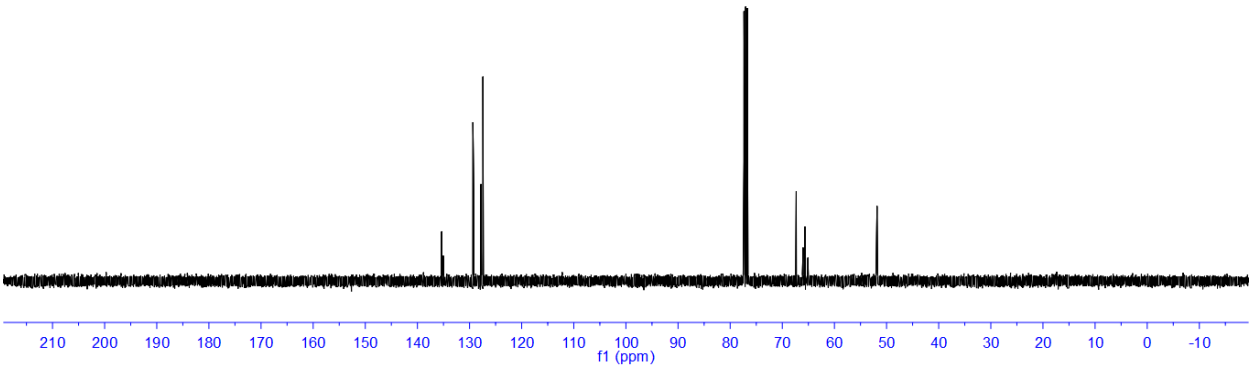

7.73
7.71
7.37
7.36
7.35
7.34
7.33
7.32
7.31
7.30
7.29
7.28
7.25
7.23
4.86
3.89
3.87
3.86
3.84
3.82
3.34
3.33
3.25
3.24
3.22
3.21
3.07
3.05
3.01
2.99
2.37
4.00
5.00
3.99
6.35
1.01
1.01
1.06
0.99
1.01
6.25
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)
NH3
(TsO)2
Ph
NH3
4b
(CD3OD, 400 MHz)

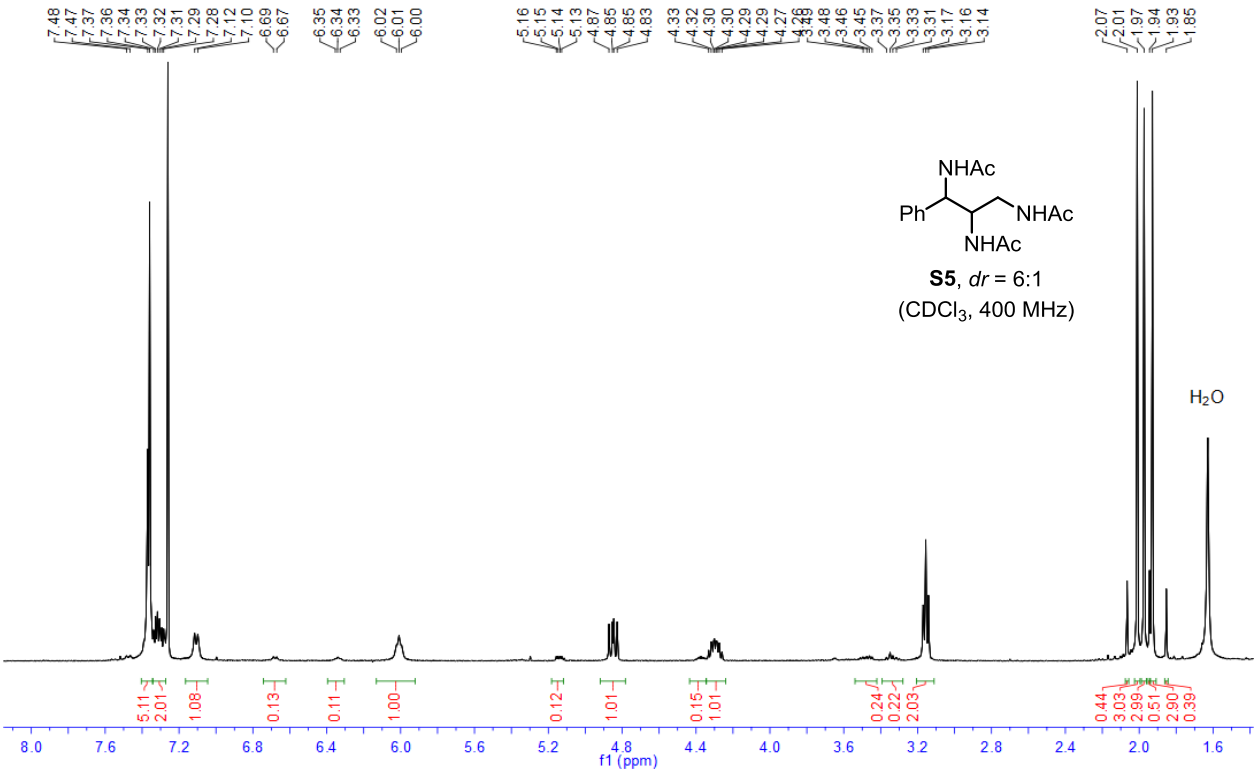

143.15
142.01
135.58
130.48
130.29
129.95
128.91
126.94
52.17
41.97
37.59
21.31
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)
NH3
(TsO)2
Ph
NH3
4b
(CD3OD, 100 MHz)

S4, *dr* = 1.8:1
($CDCl_3$, 400 MHz)

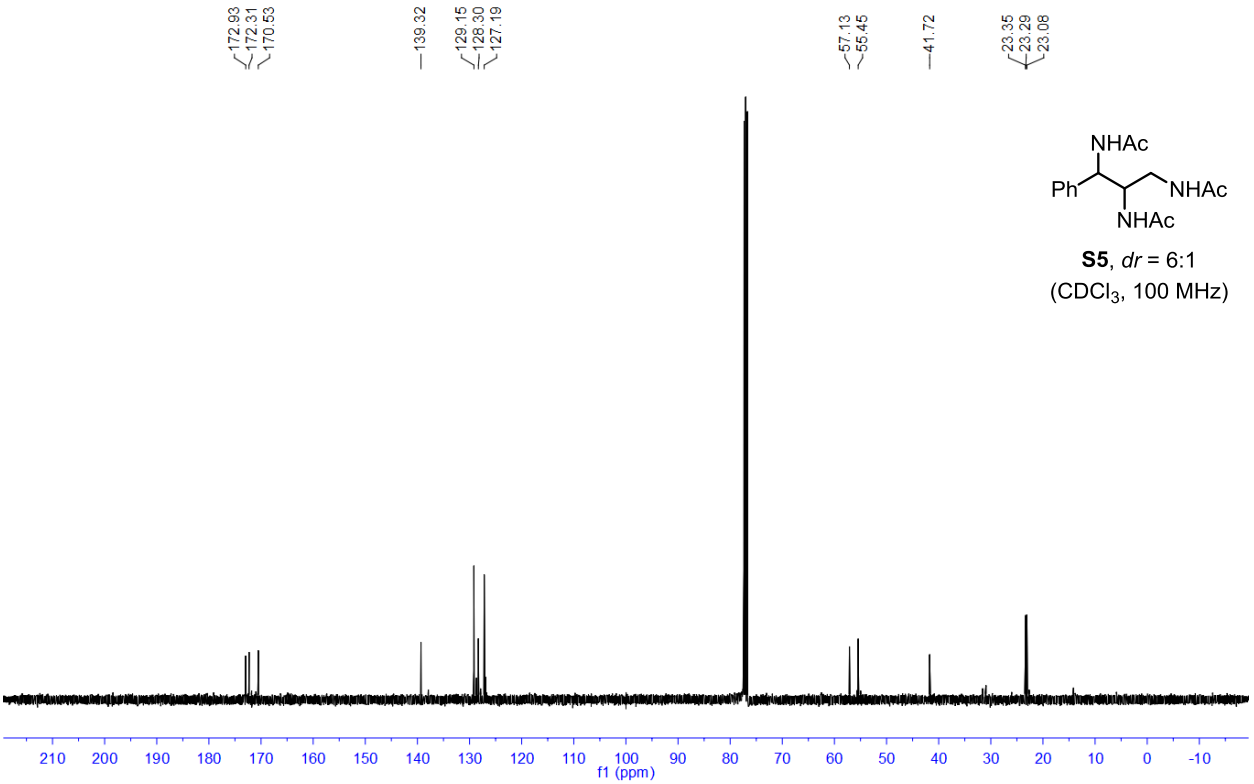


S4, *dr* = 1.8:1
($CDCl_3$, 100 MHz)

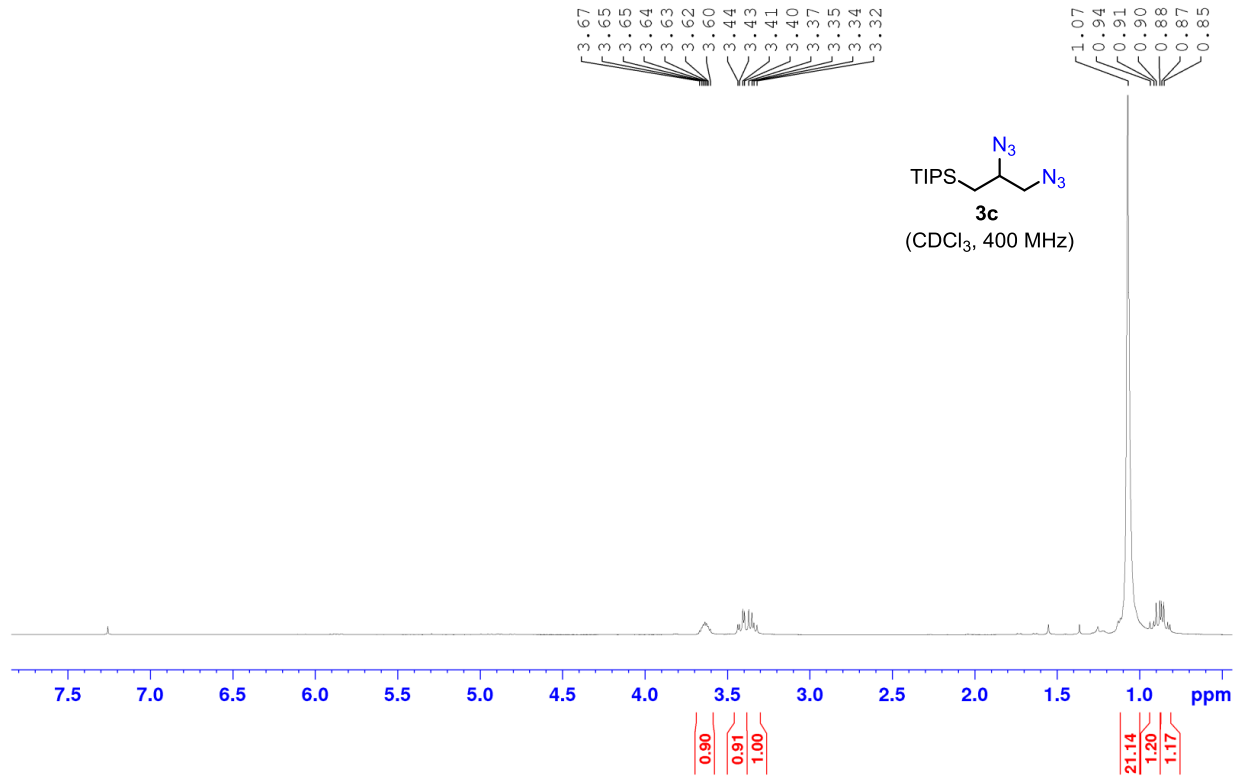


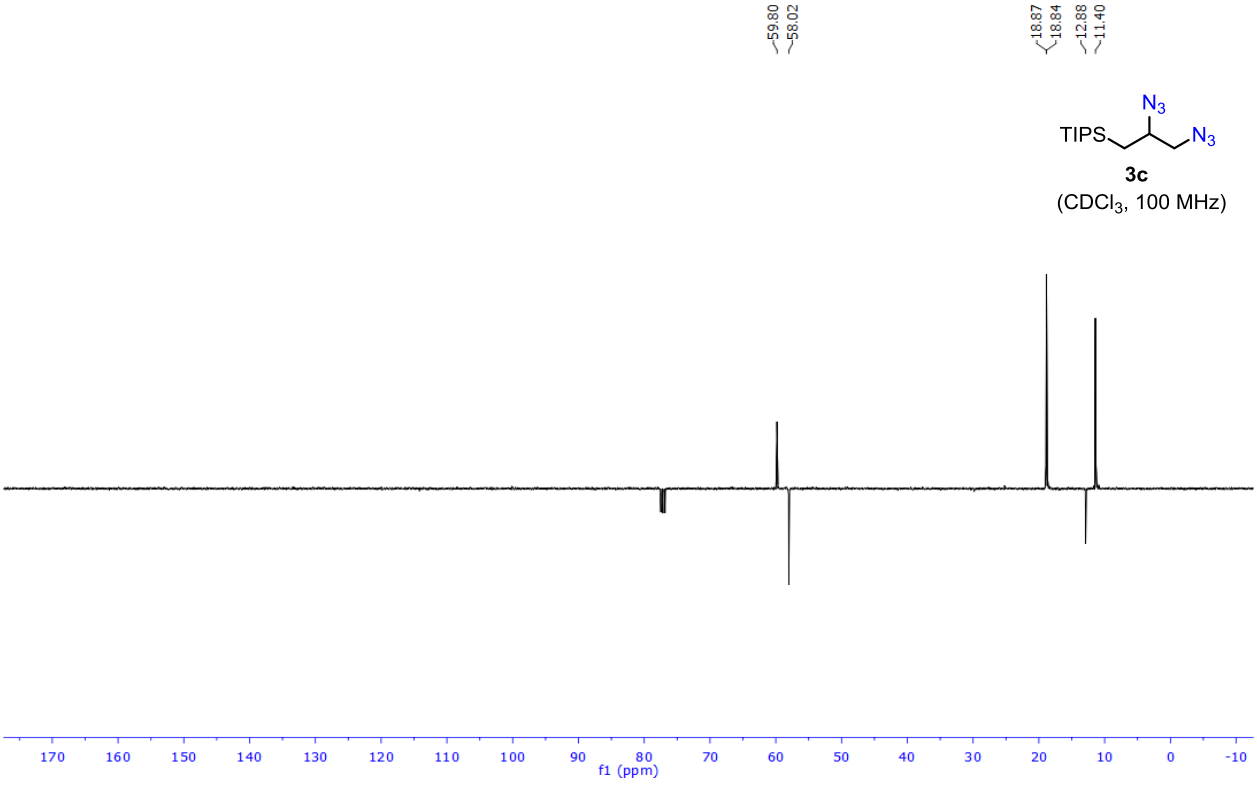


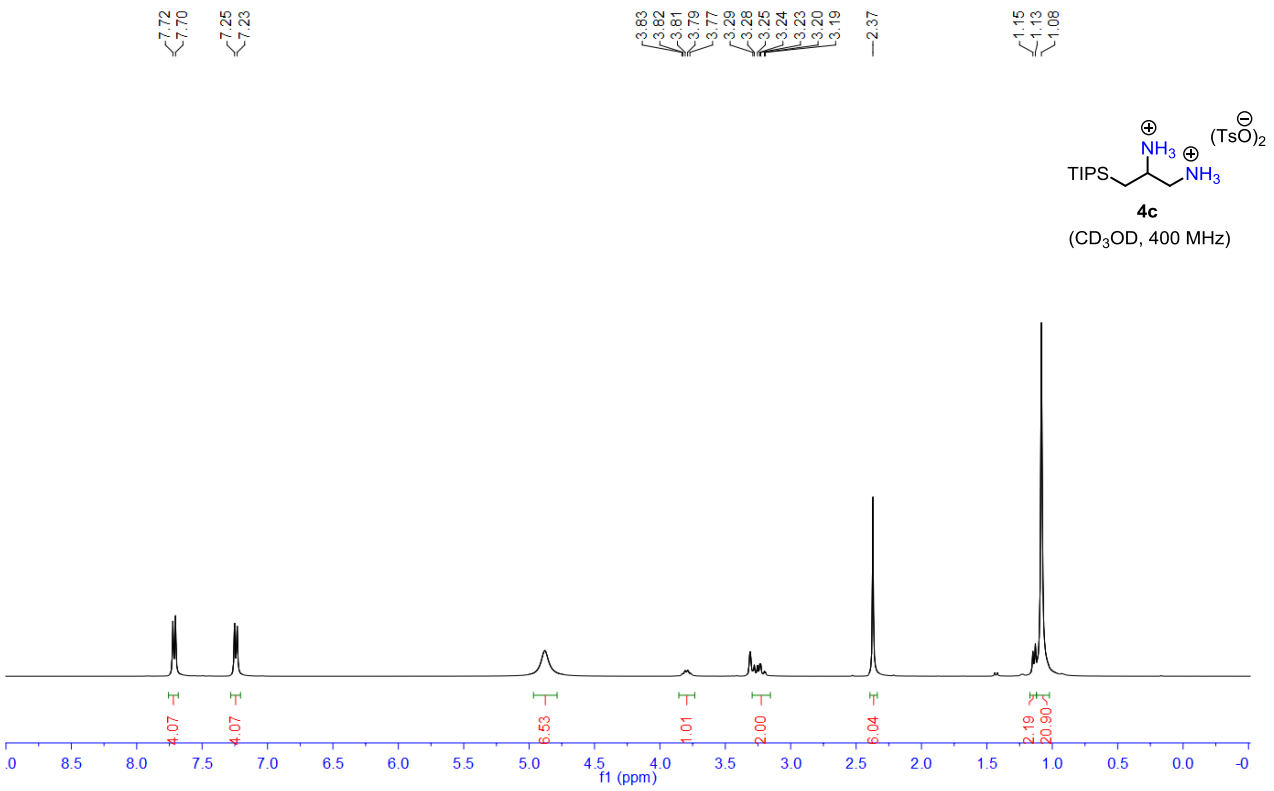
S5, *dr* = 6:1
($CDCl_3$, 400 MHz)

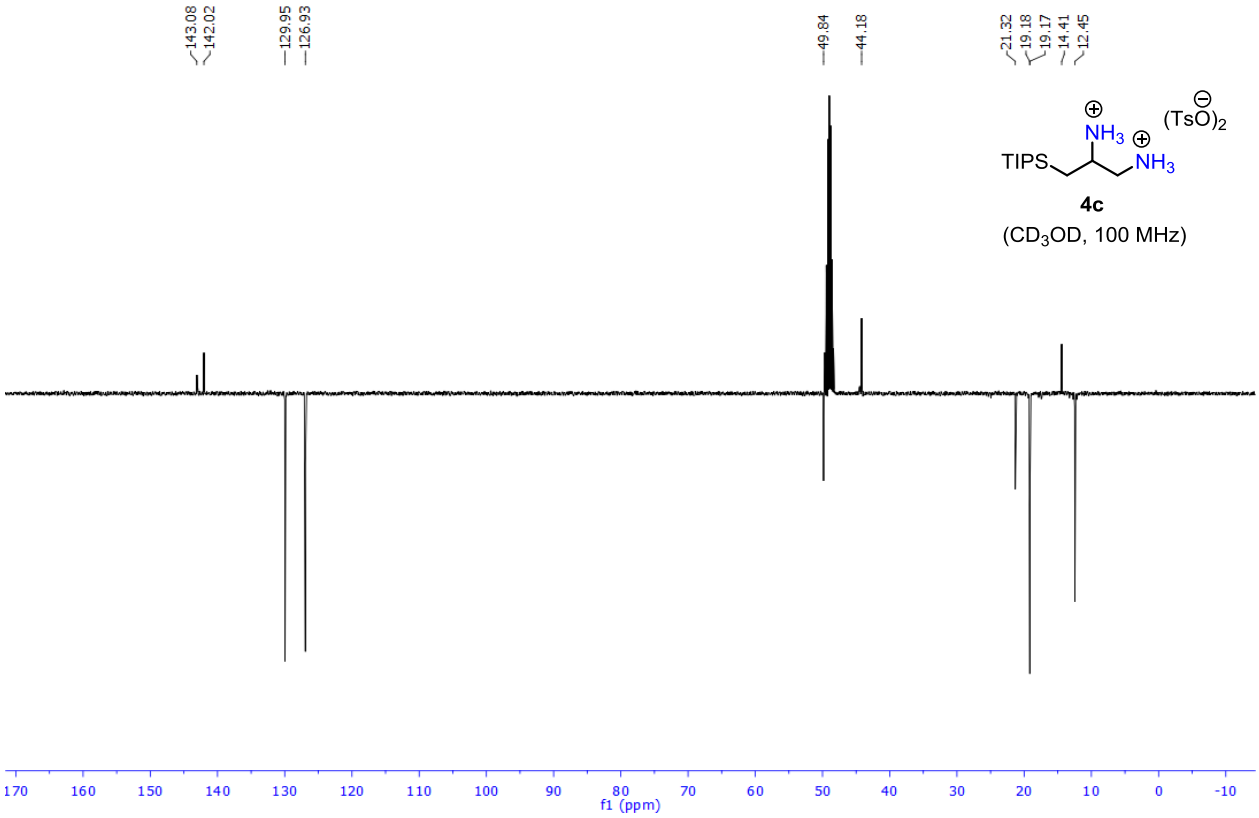


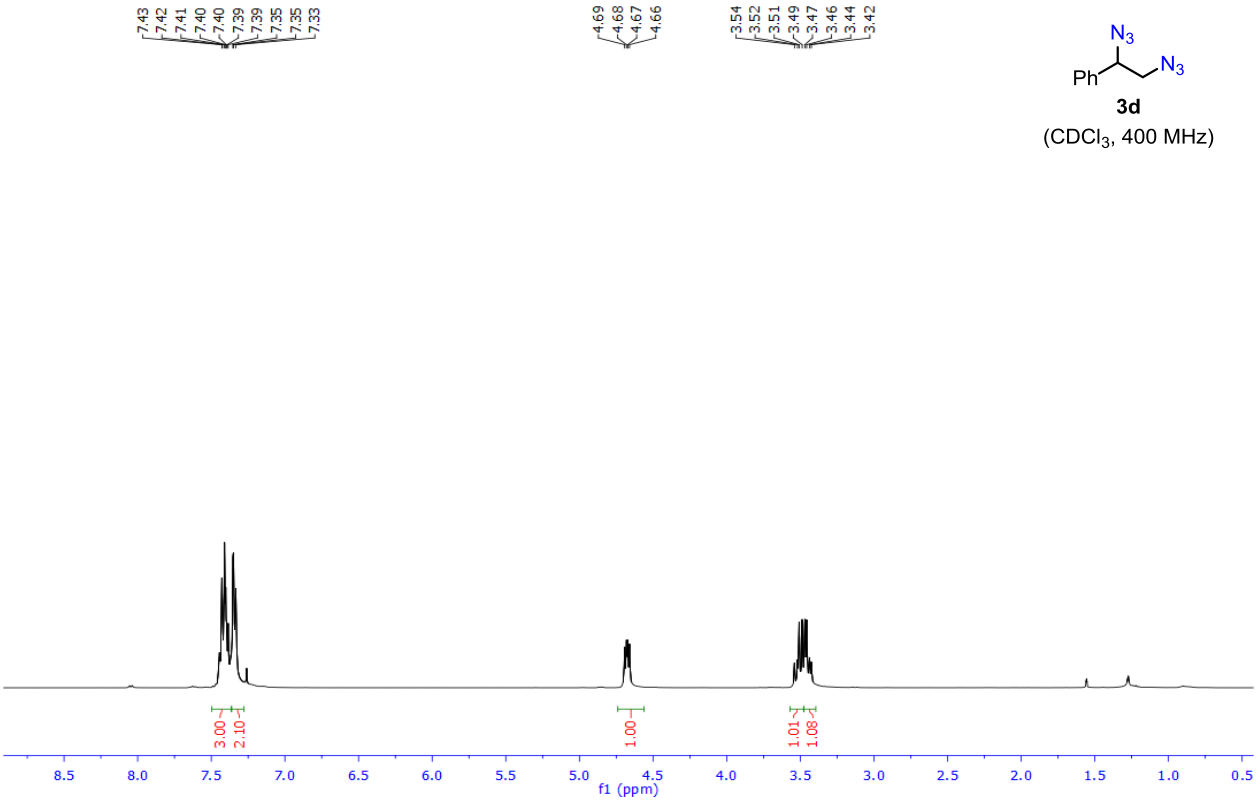
S5, *dr* = 6:1
($CDCl_3$, 100 MHz)

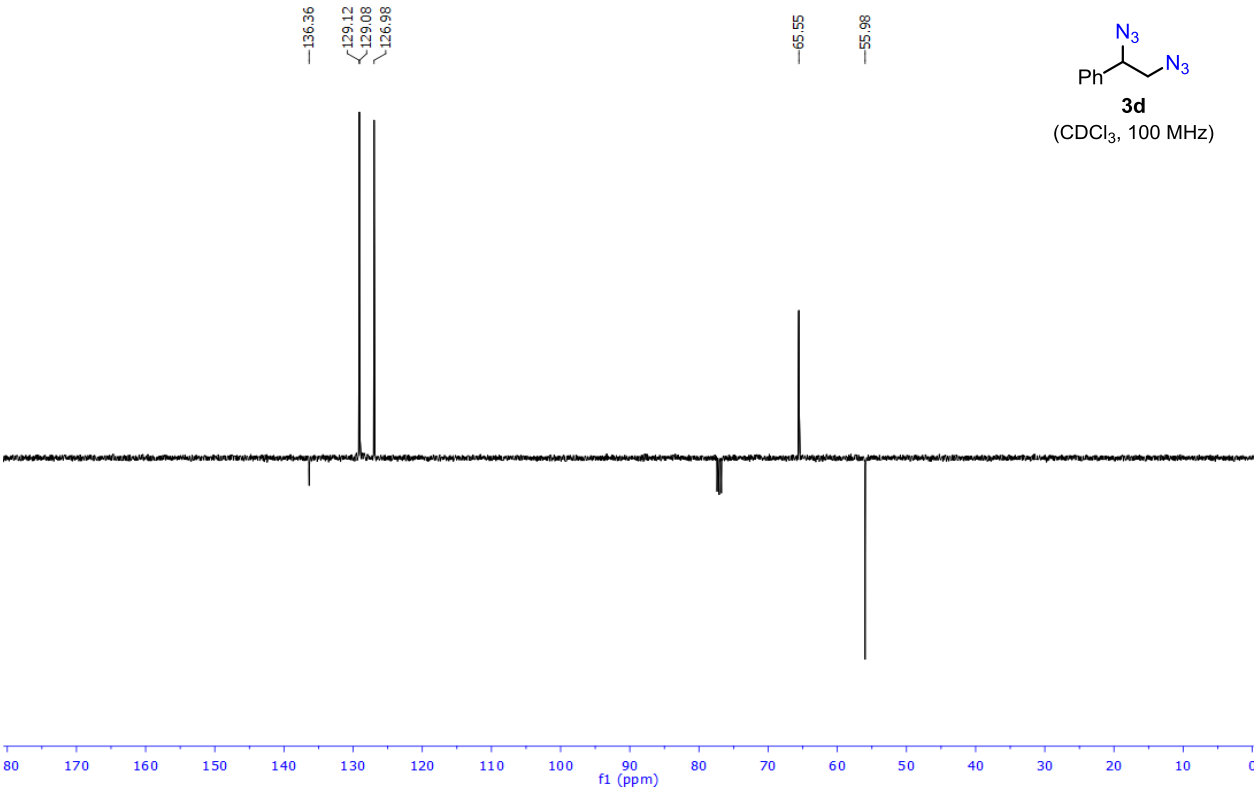

3.67
3.65
3.65
3.64
3.63
3.62
3.60
3.44
3.43
3.41
3.40
3.37
3.35
3.34
3.32
1.07
0.94
0.91
0.90
0.88
0.87
0.85
N3
TIPS
N3
3c
(CDCl3, 400 MHz)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
0.90
0.91
1.00
21.14
1.20
1.17

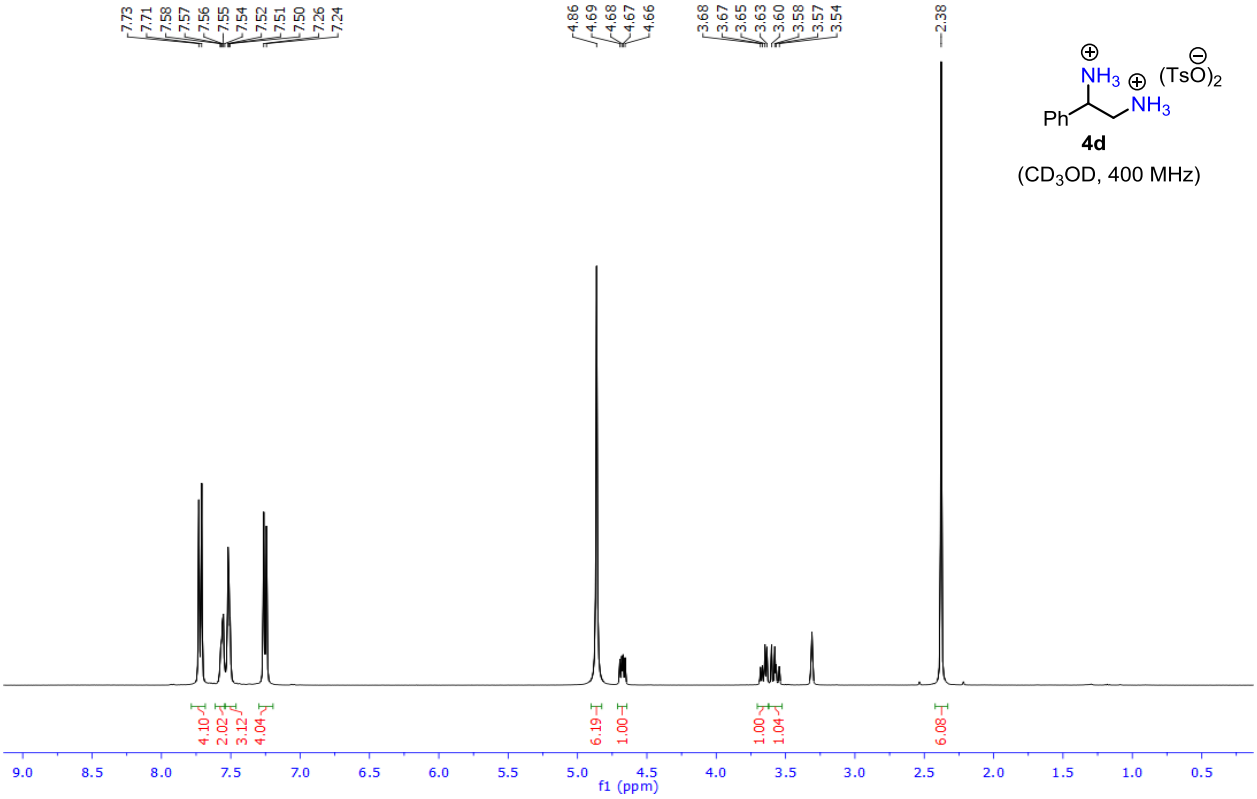

59.80
58.02
18.87
18.84
12.88
11.40
N3
TIPS
N3
3c
(CDCl3, 100 MHz)
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


7.72
7.70
7.25
7.23
3.83
3.82
3.81
3.79
3.77
3.29
3.28
3.25
3.24
3.23
3.20
3.19
2.37
1.15
1.13
1.08
NH3
(TsO)2
TIPS
NH3
4c
(CD3OD, 400 MHz)
4.07
4.07
6.53
1.01
2.00
6.04
2.19
20.90
f1 (ppm)


143.08
142.02
129.95
126.93
49.84
44.18
21.32
19.18
19.17
14.41
12.45
NH3
(TsO)2
TIPS
NH3
4c
(CD3OD, 100 MHz)
f1 (ppm)

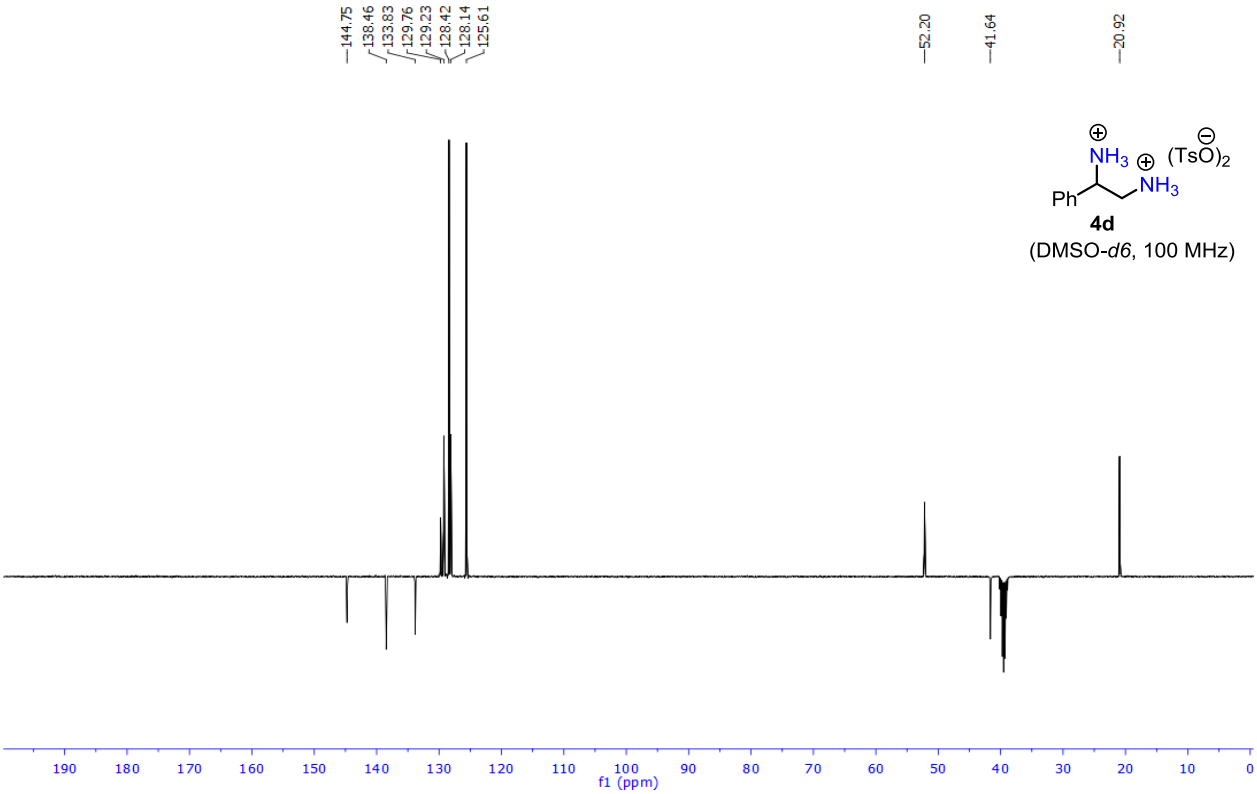

7.43
7.42
7.41
7.40
7.40
7.39
7.39
7.35
7.35
7.33
4.69
4.68
4.67
4.66
3.54
3.52
3.51
3.49
3.47
3.46
3.44
3.42
N3
Ph
N3
3d
(CDCl3, 400 MHz)
3.00
2.10
1.00
1.01
1.08
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


136.36
129.12
129.08
126.98
65.55
55.98
N3
Ph
N3
3d
(CDCl3, 100 MHz)
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)



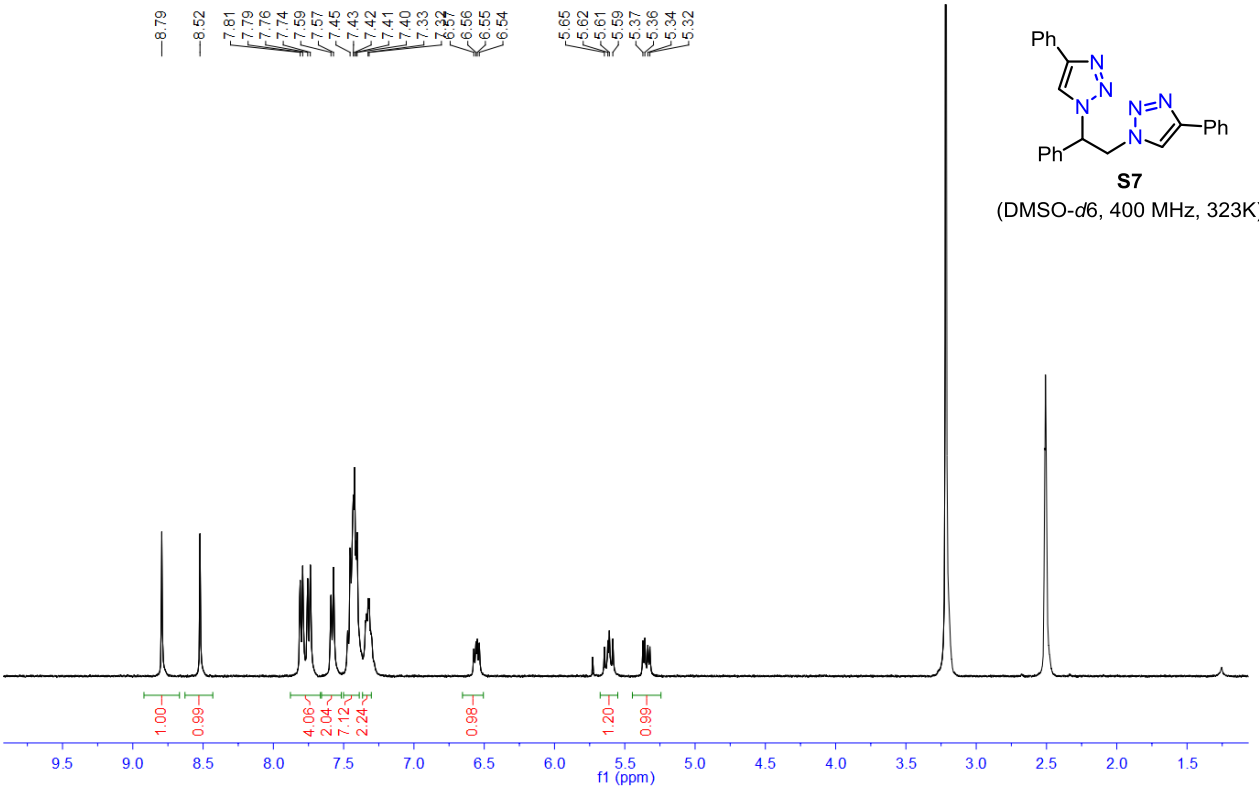
4d

(CD_3OD, 400 MHz)



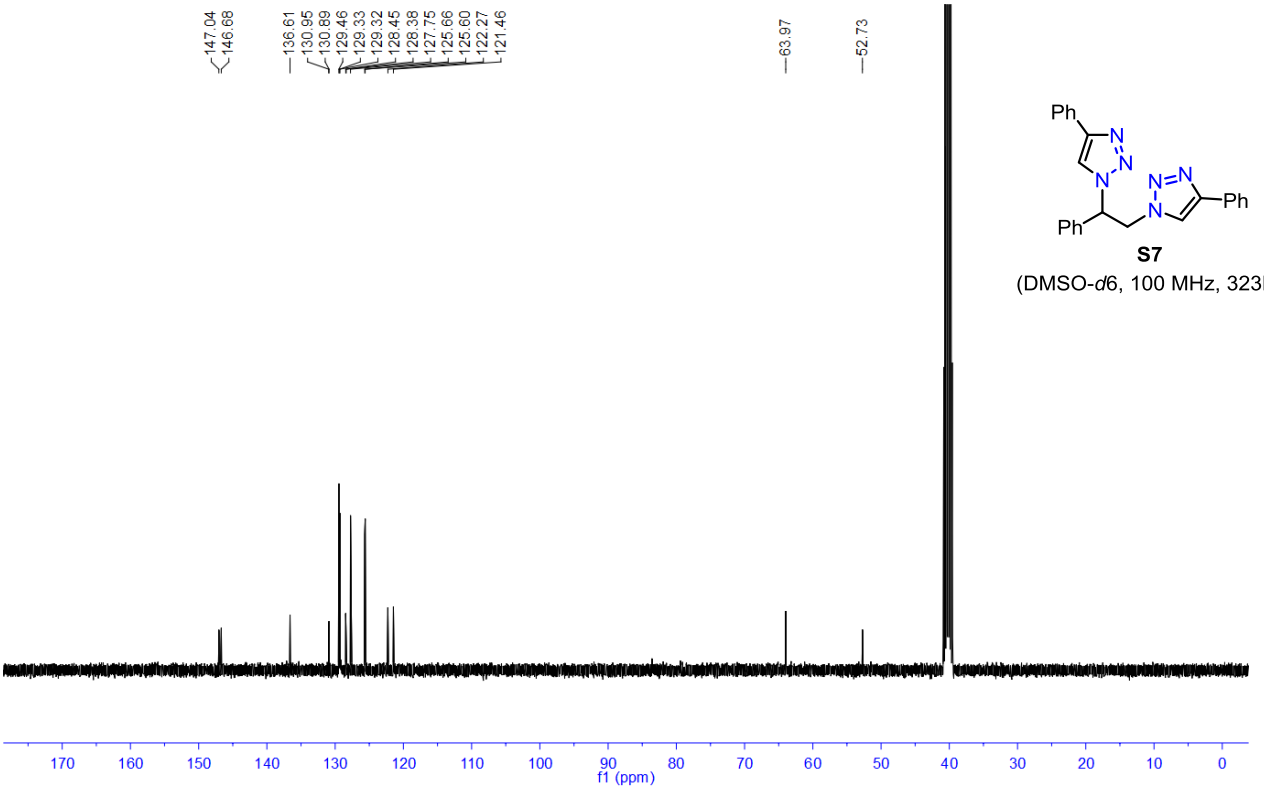
4d

(DMSO-*d6*, 100 MHz)



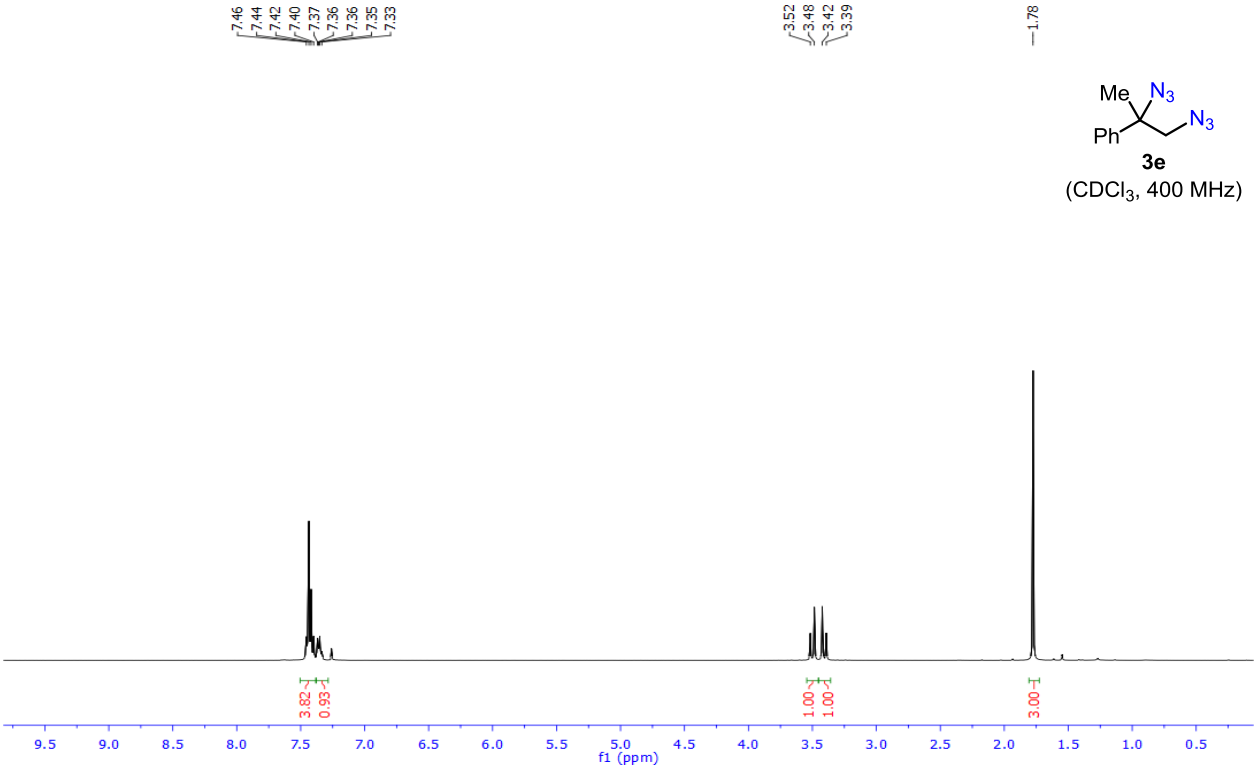
S7

(DMSO-*d*6, 400 MHz, 323K)



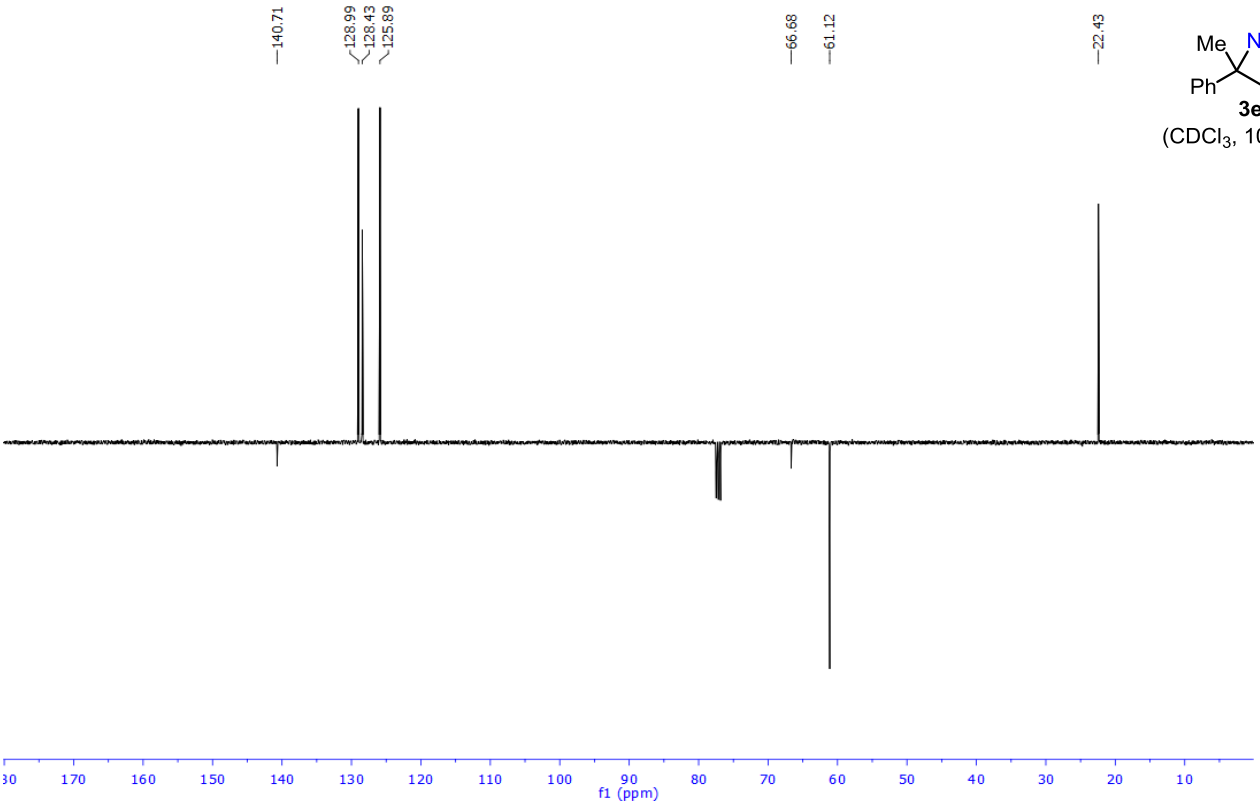
S7

(DMSO-*d*6, 100 MHz, 323K)



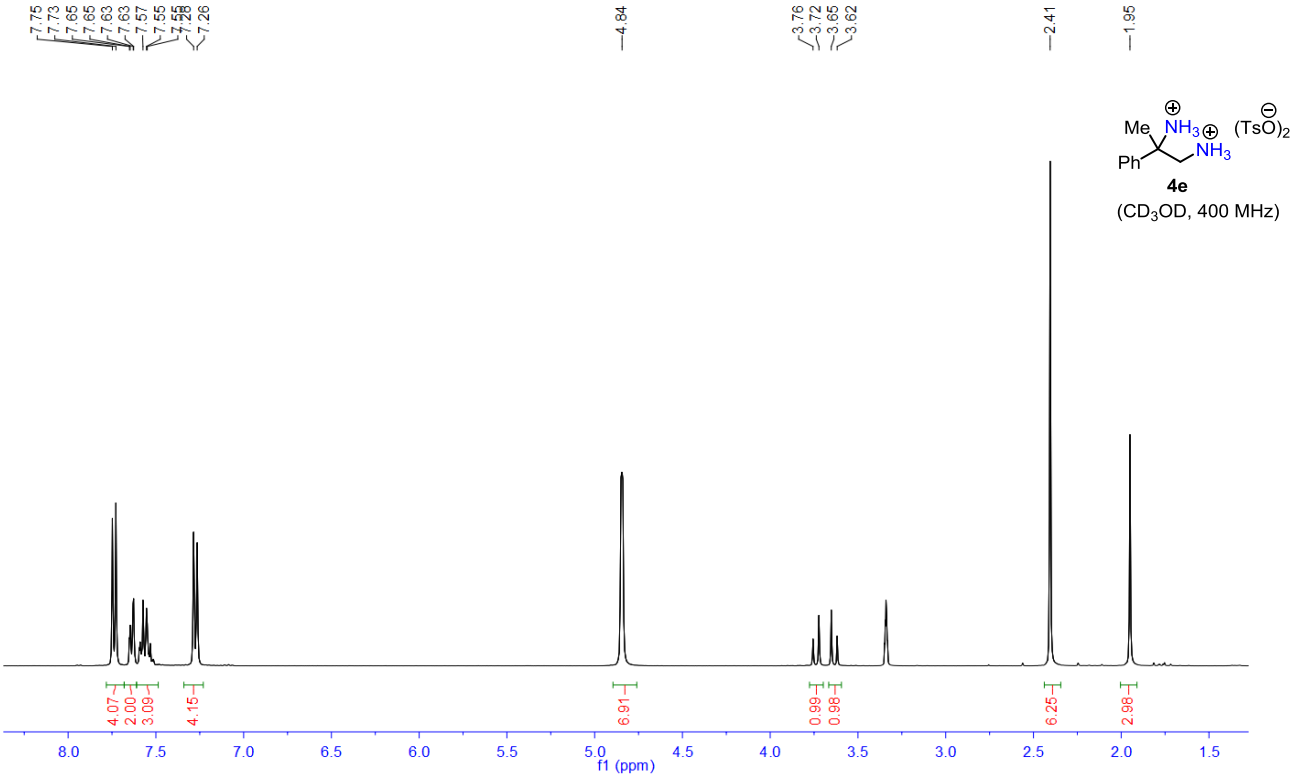
3e

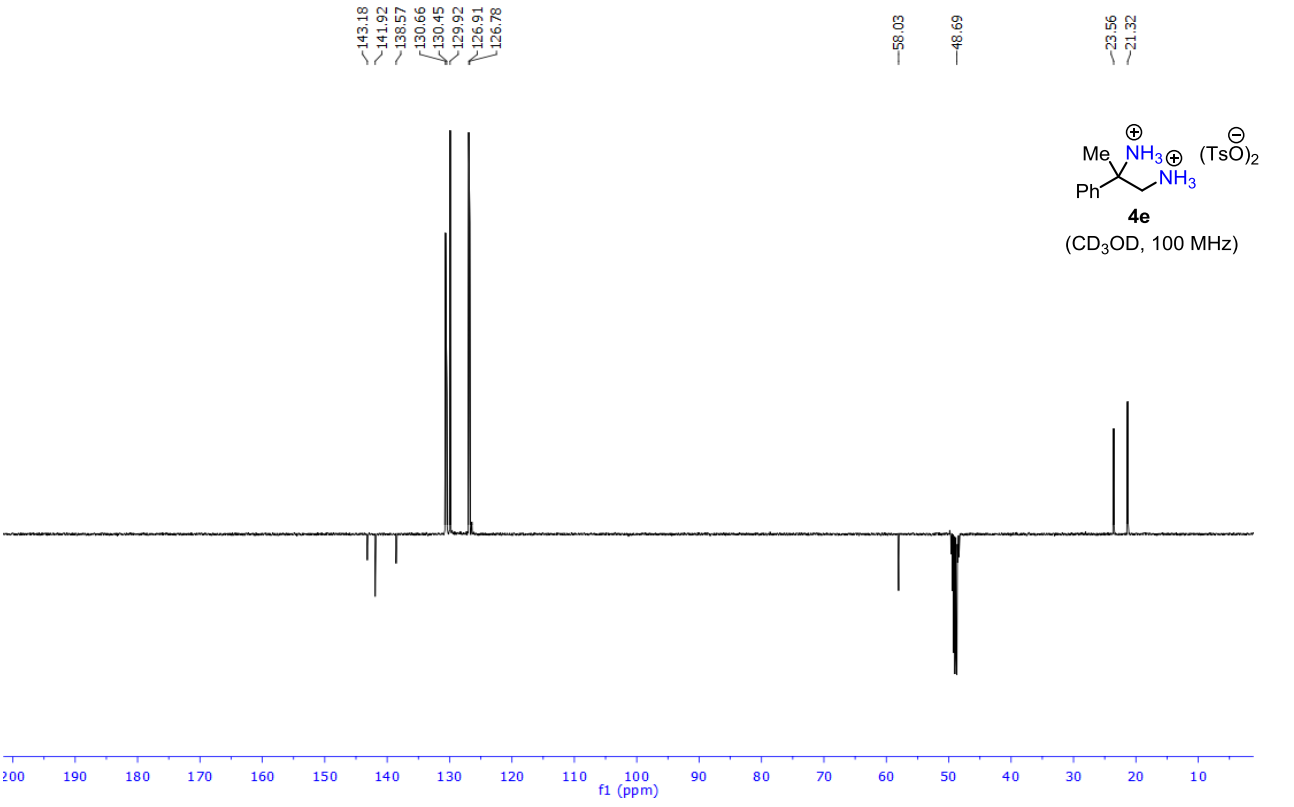
($CDCl_3$, 400 MHz)

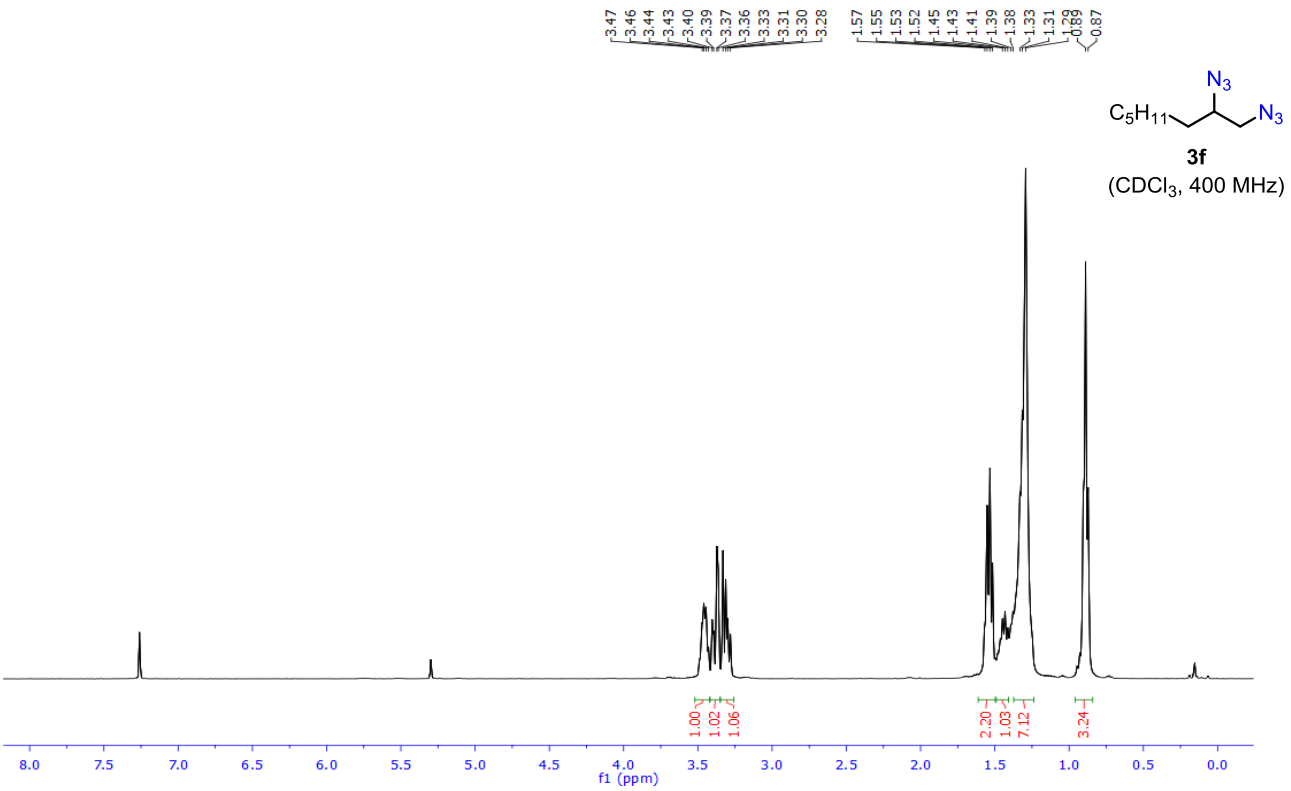


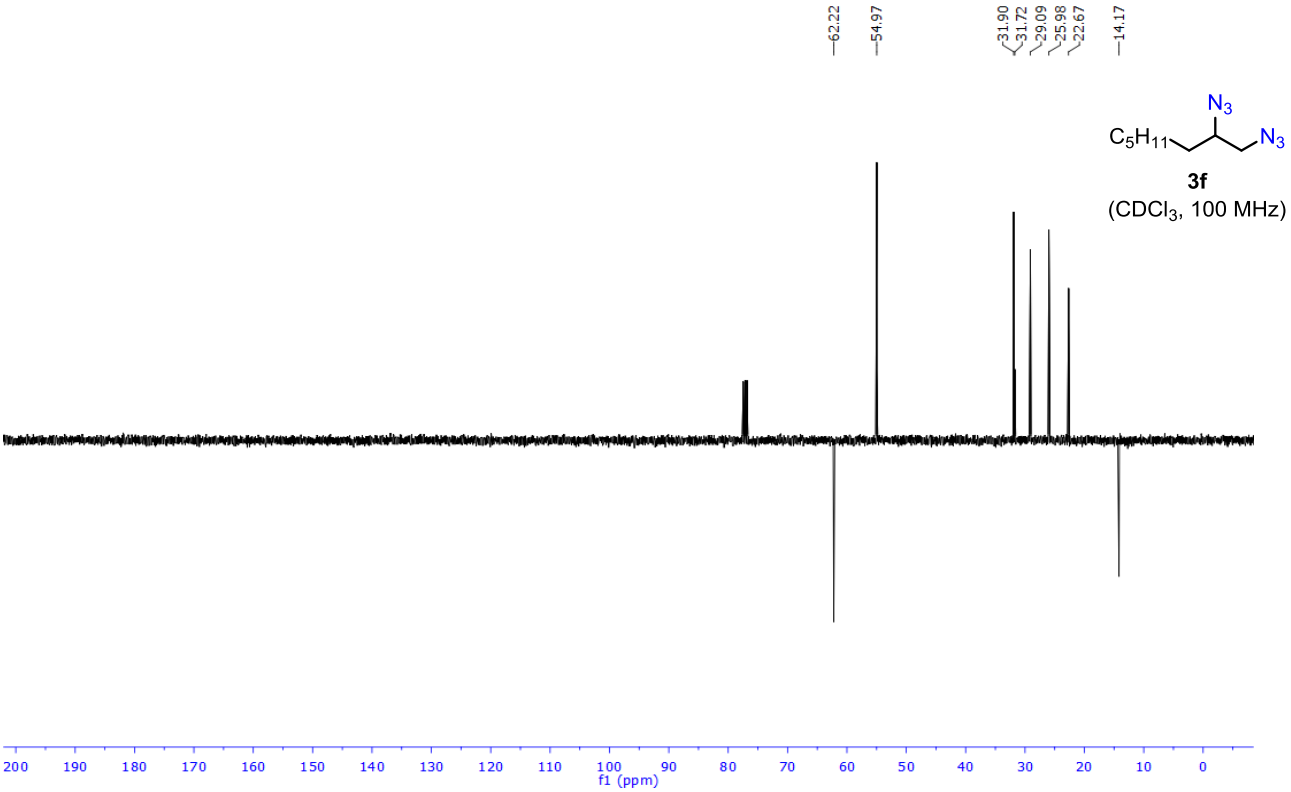
3e

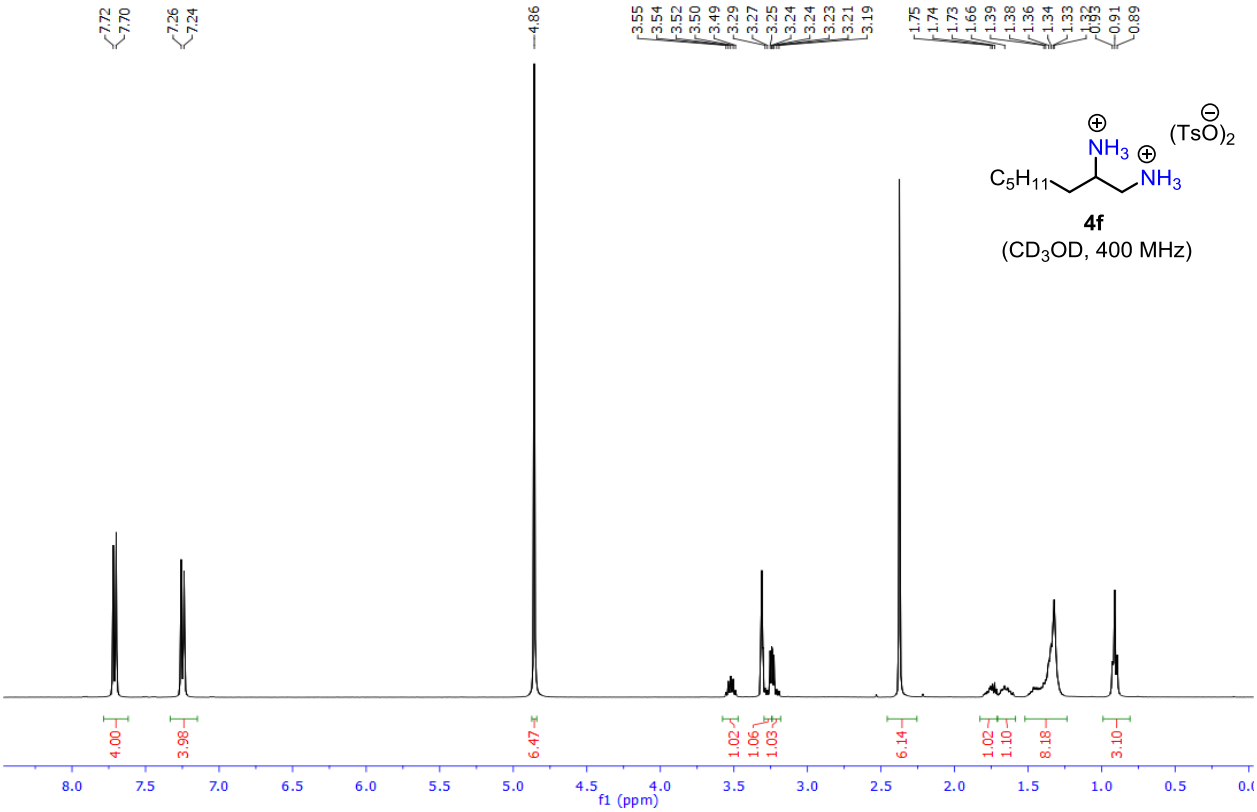
($CDCl_3$, 100 MHz)

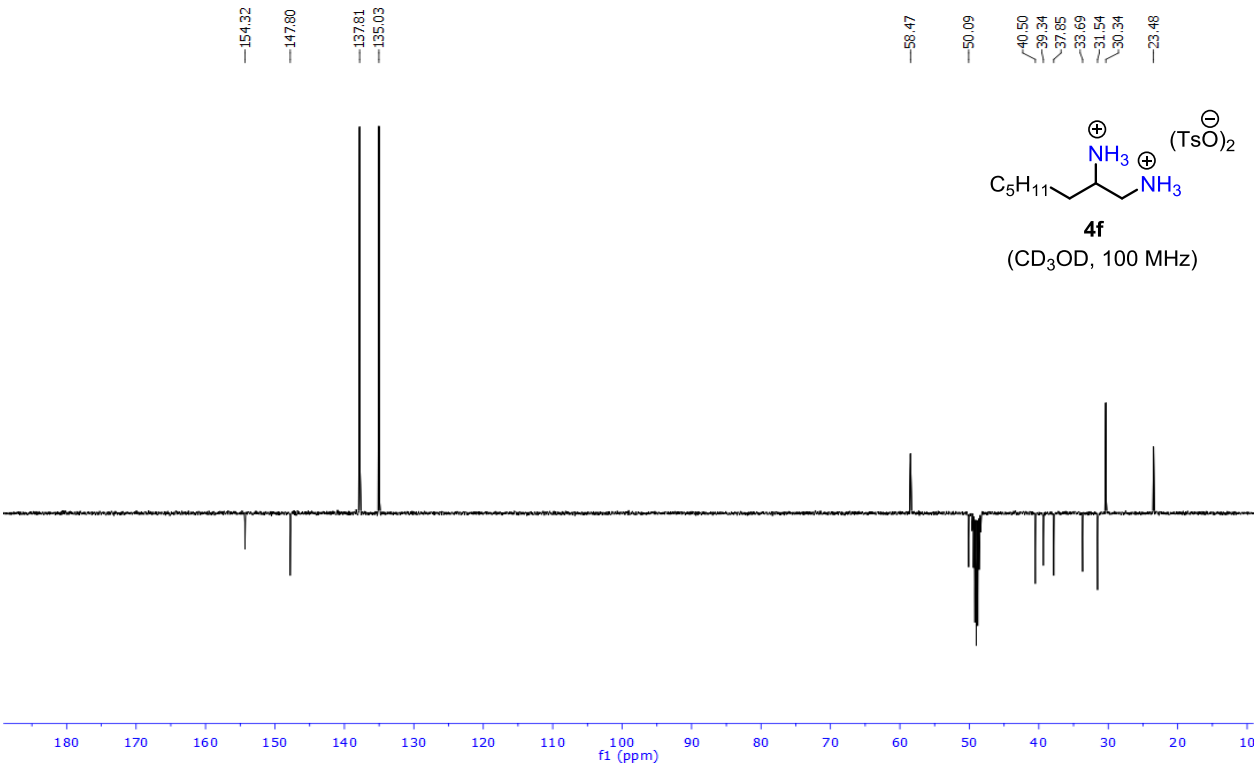

7.75
7.73
7.65
7.65
7.63
7.63
7.57
7.55
7.55
7.28
7.26
4.84
3.76
3.72
3.65
3.62
2.41
1.95
Me
NH3
NH3
Ph
(TsO)2
4e
(CD3OD, 400 MHz)
4.07
2.00
3.09
4.15
6.91
0.99
0.98
6.25
2.98
f1 (ppm)

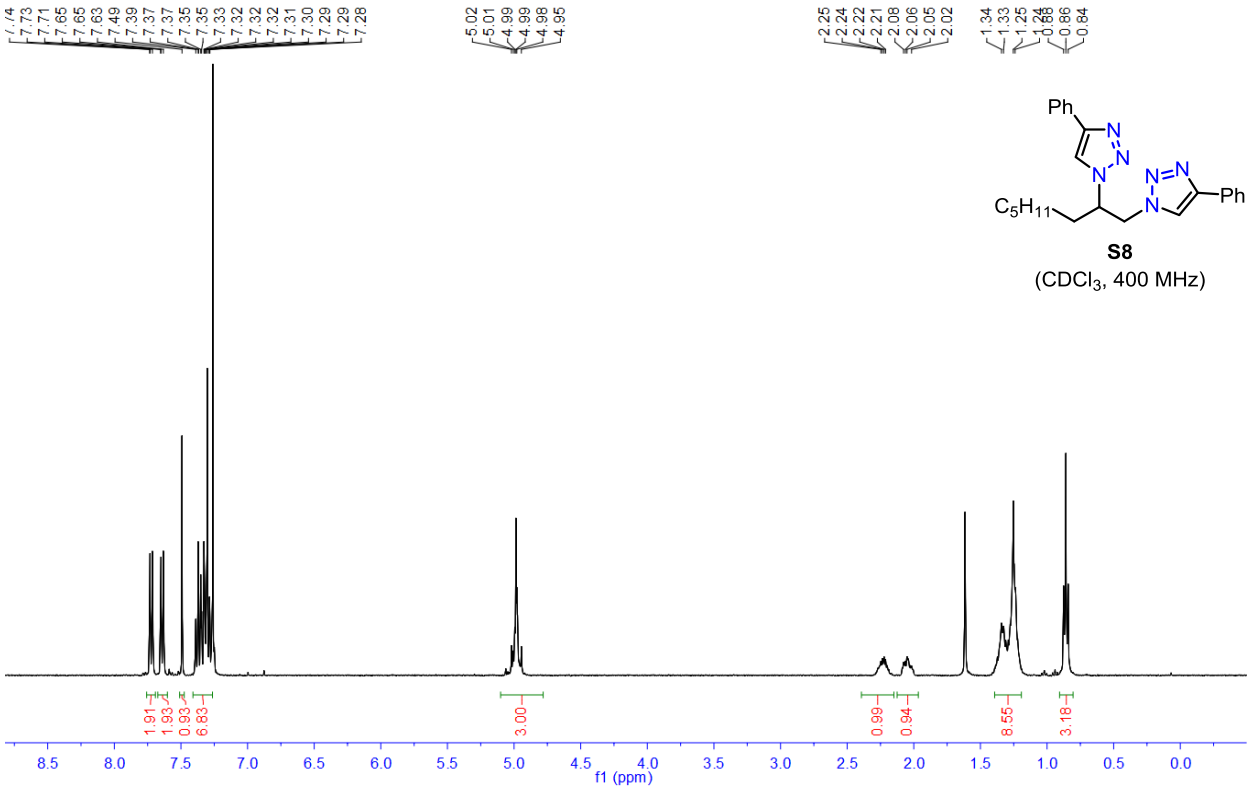

143.18
141.92
138.57
130.66
130.45
129.92
126.91
126.78
58.03
48.69
23.56
21.32
Me
NH3
NH3
Ph
(TsO)2
4e
(CD3OD, 100 MHz)
f1 (ppm)


3.47
3.46
3.44
3.43
3.40
3.39
3.37
3.36
3.33
3.31
3.30
3.28
1.57
1.55
1.53
1.52
1.45
1.43
1.41
1.39
1.38
1.33
1.31
1.29
0.89
0.87
N3
C5H11
N3
3f
(CDCl3, 400 MHz)
1.00
1.02
1.06
2.20
1.03
7.12
3.24
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


62.22
54.97
31.90
31.72
29.09
25.98
22.67
14.17
N3
C5H11
N3
3f
(CDCl3, 100 MHz)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

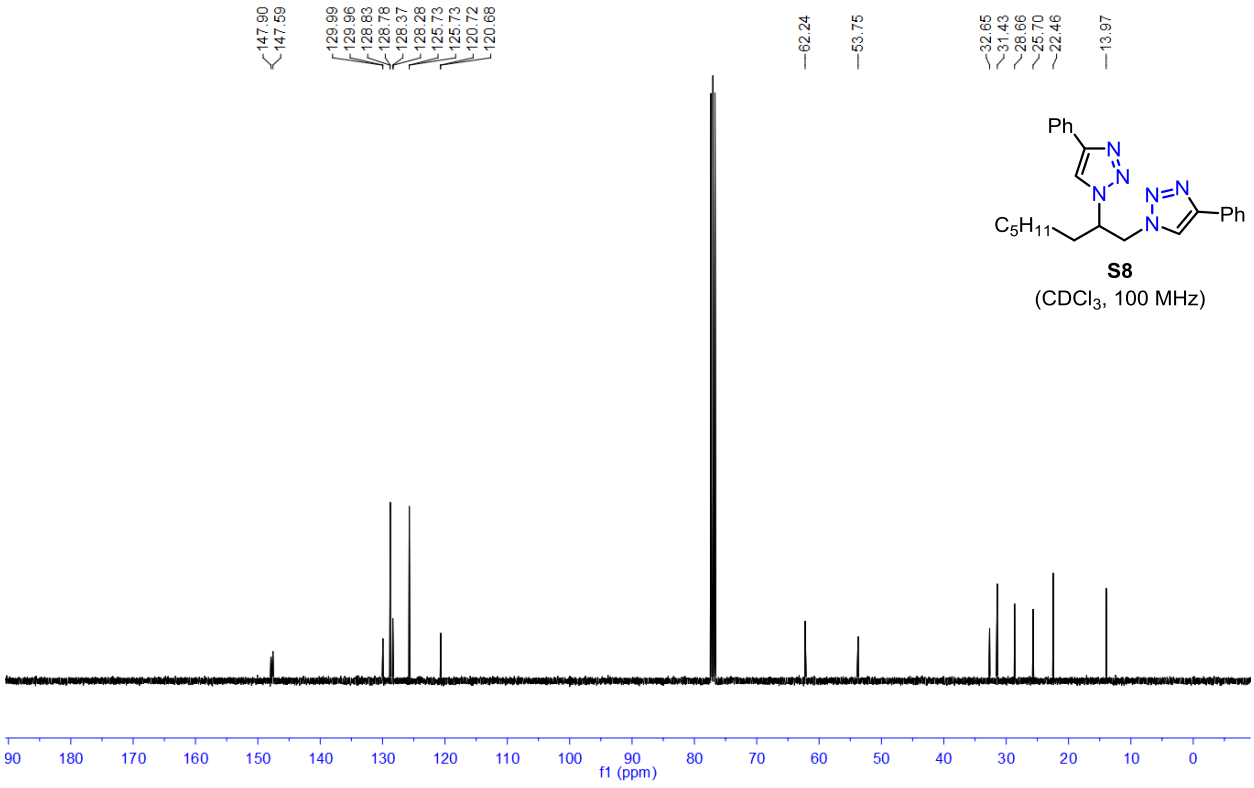

7.72
7.70
7.26
7.24
4.86
3.55
3.54
3.52
3.50
3.49
3.29
3.27
3.25
3.24
3.24
3.23
3.21
3.19
1.75
1.74
1.73
1.66
1.39
1.38
1.36
1.34
1.33
0.93
0.91
0.89
NH3
NH3
C5H11
(TsO)2
4f
(CD3OD, 400 MHz)
4.00
3.98
6.47
1.02
1.06
1.03
6.14
1.02
1.10
8.18
3.10
f1 (ppm)


154.32
147.80
137.81
135.03
58.47
50.09
40.50
39.34
37.85
33.69
31.54
30.34
23.48
NH3
NH3
C5H11
(TsO)2
4f
(CD3OD, 100 MHz)
f1 (ppm)



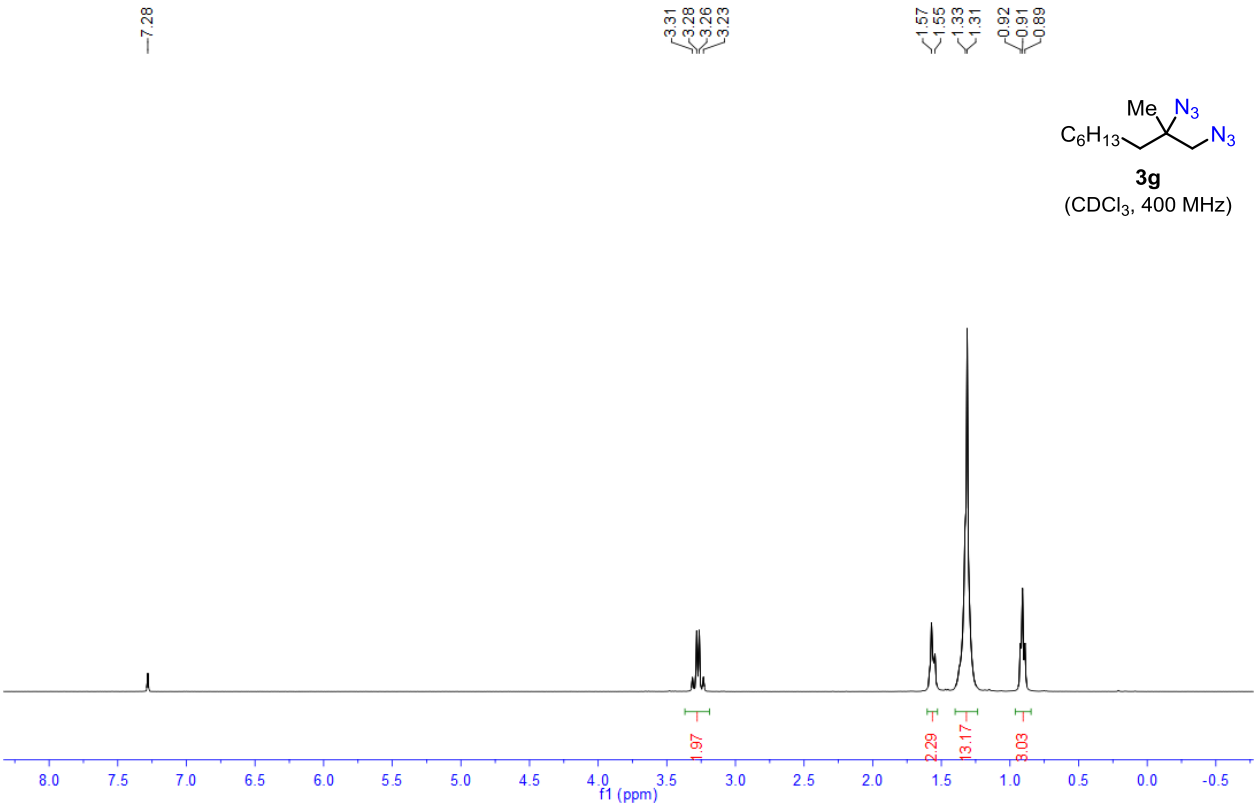
S8

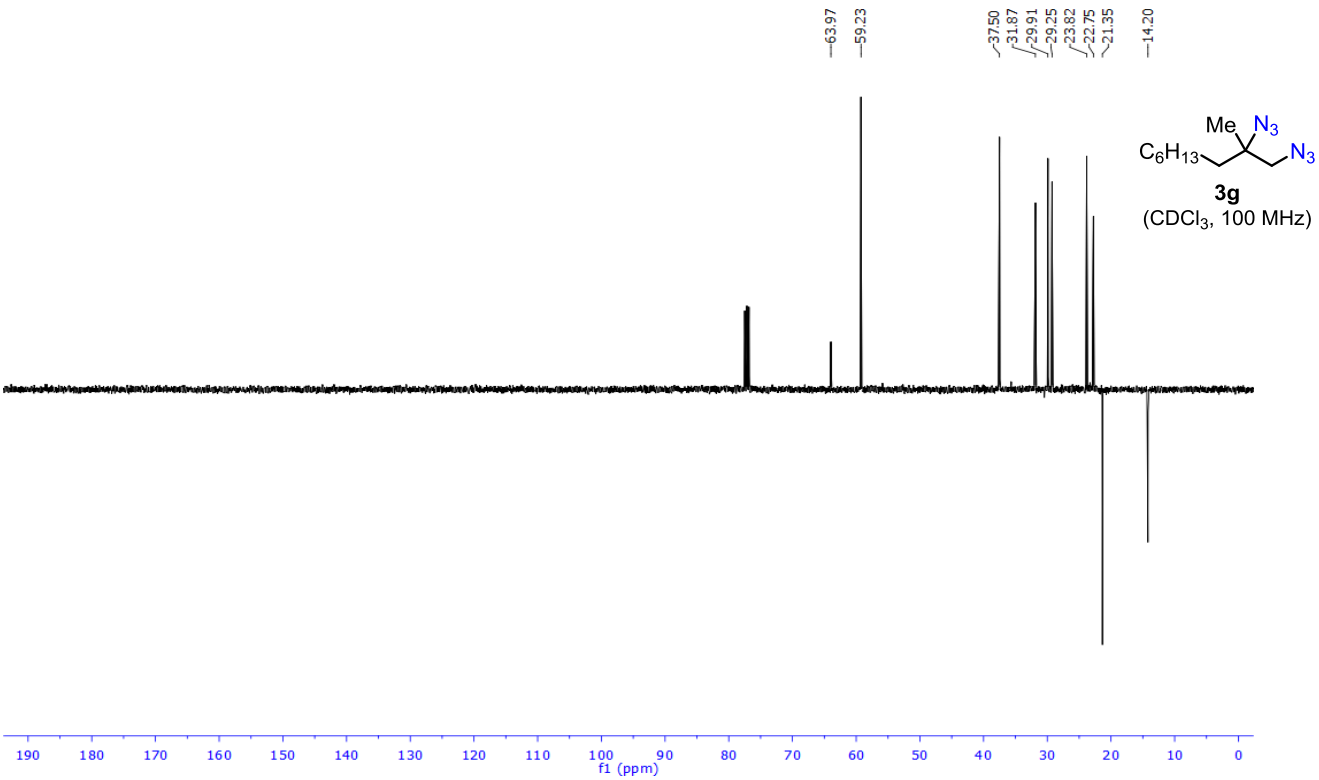
($CDCl_3$, 400 MHz)

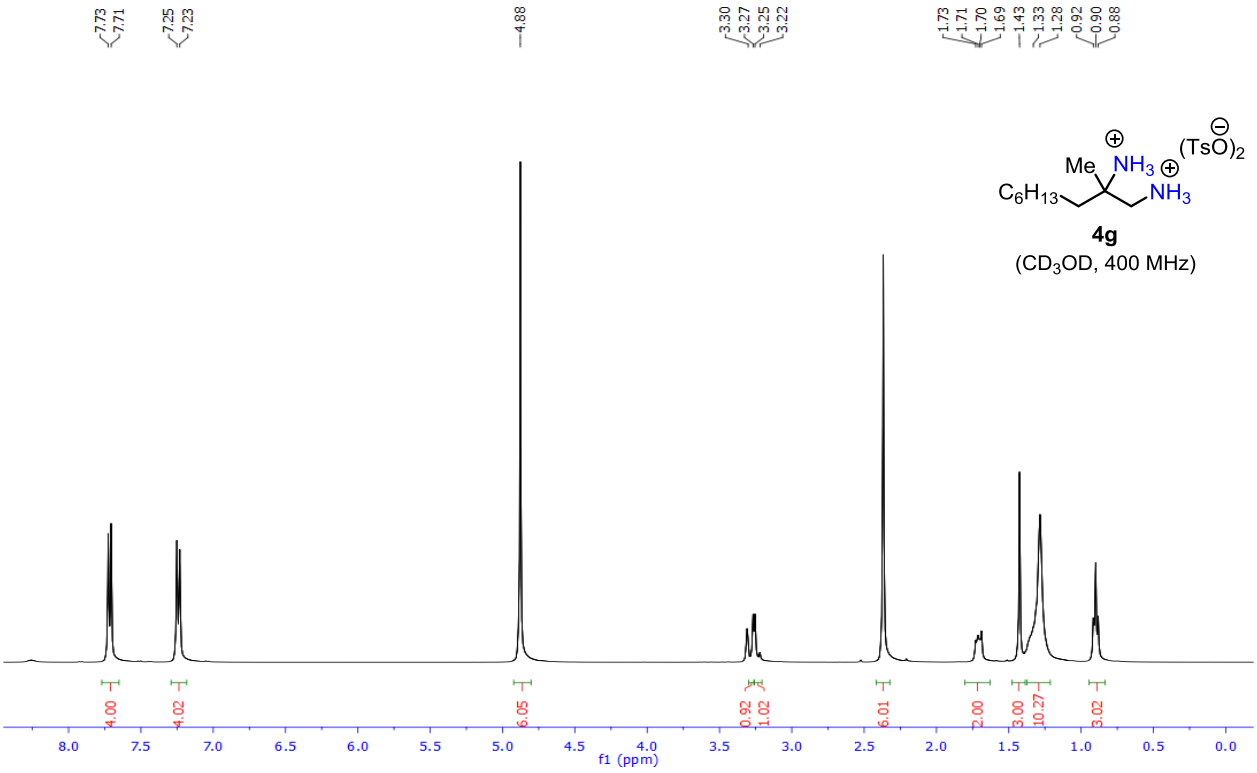


S8

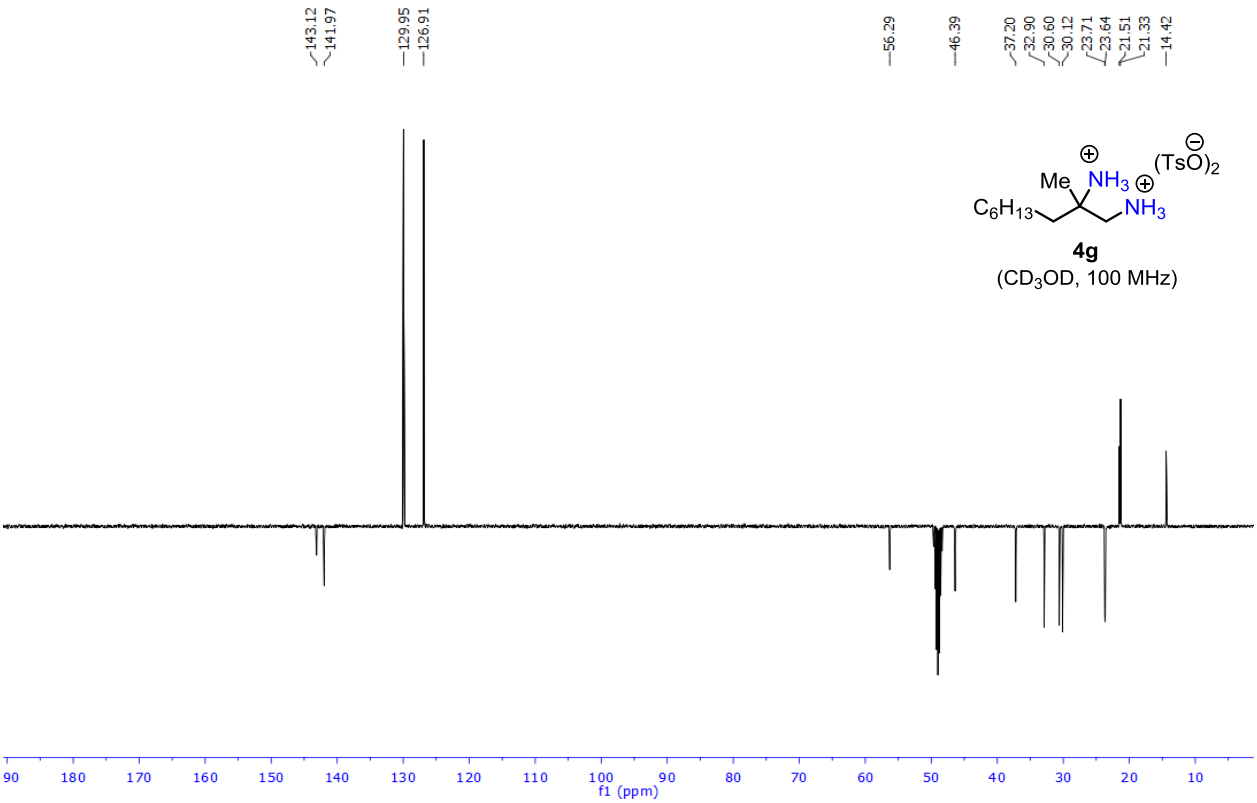
($CDCl_3$, 100 MHz)


7.28
3.31
3.28
3.26
3.23
1.57
1.55
1.33
1.31
0.92
0.91
0.89
Me
N3
C6H13
N3
3g
(CDCl3, 400 MHz)
1.97
2.29
13.17
8.03
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

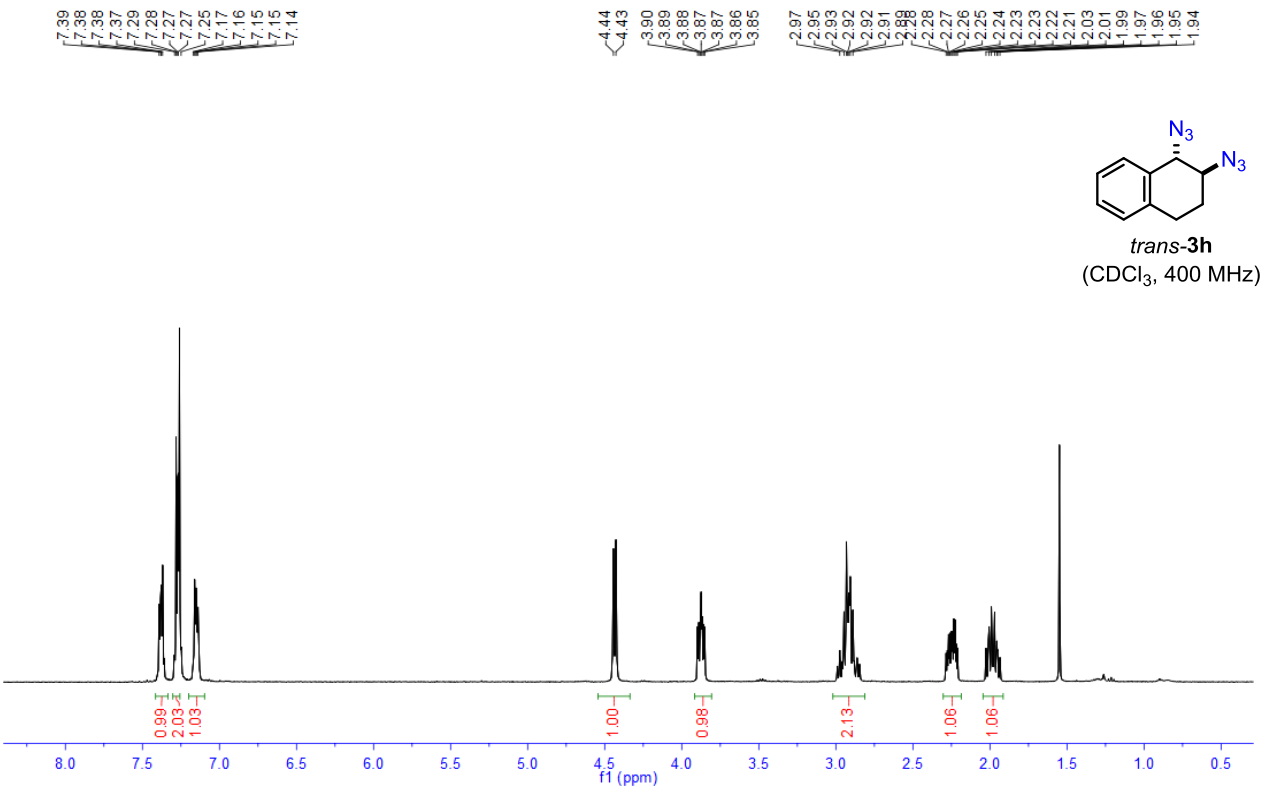

63.97
59.23
37.50
31.87
29.91
29.25
23.82
22.75
21.35
14.20
Me
N3
C6H13
N3
3g
(CDCl3, 100 MHz)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



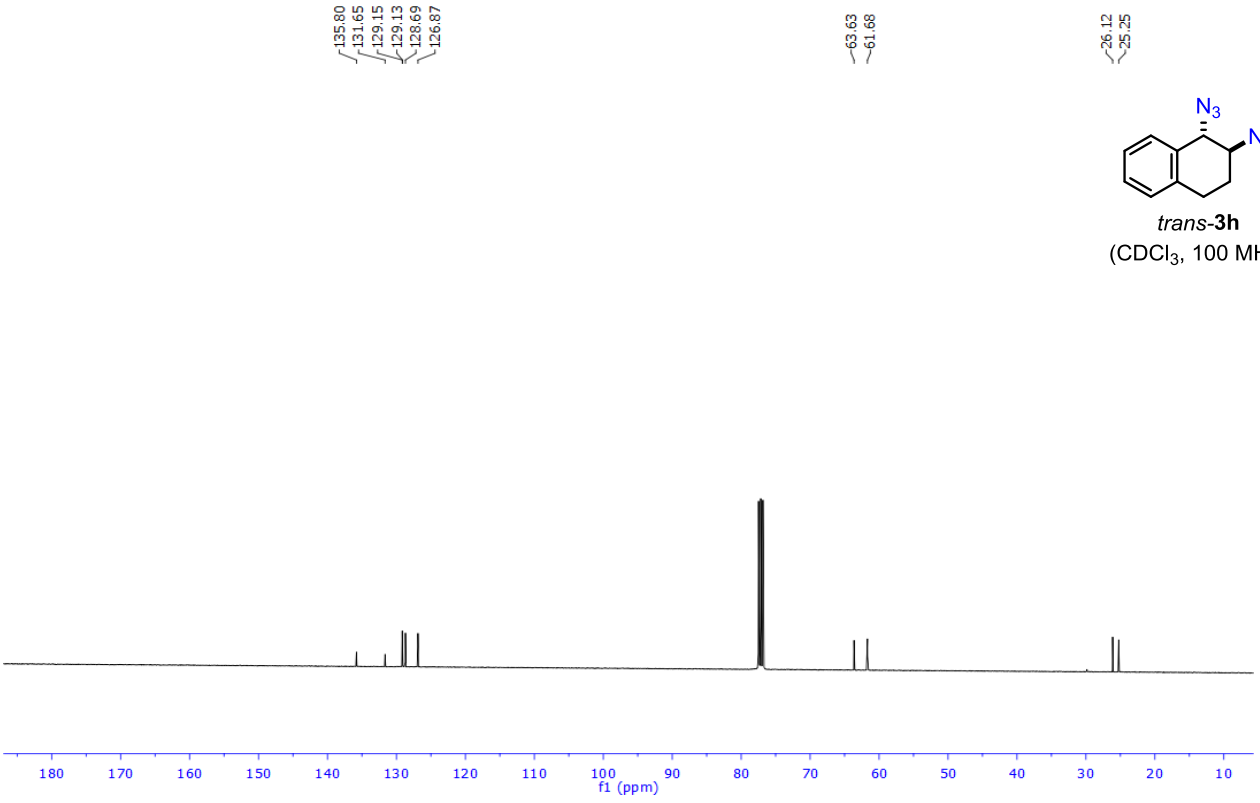
4g
(CD_3OD, 400 MHz)



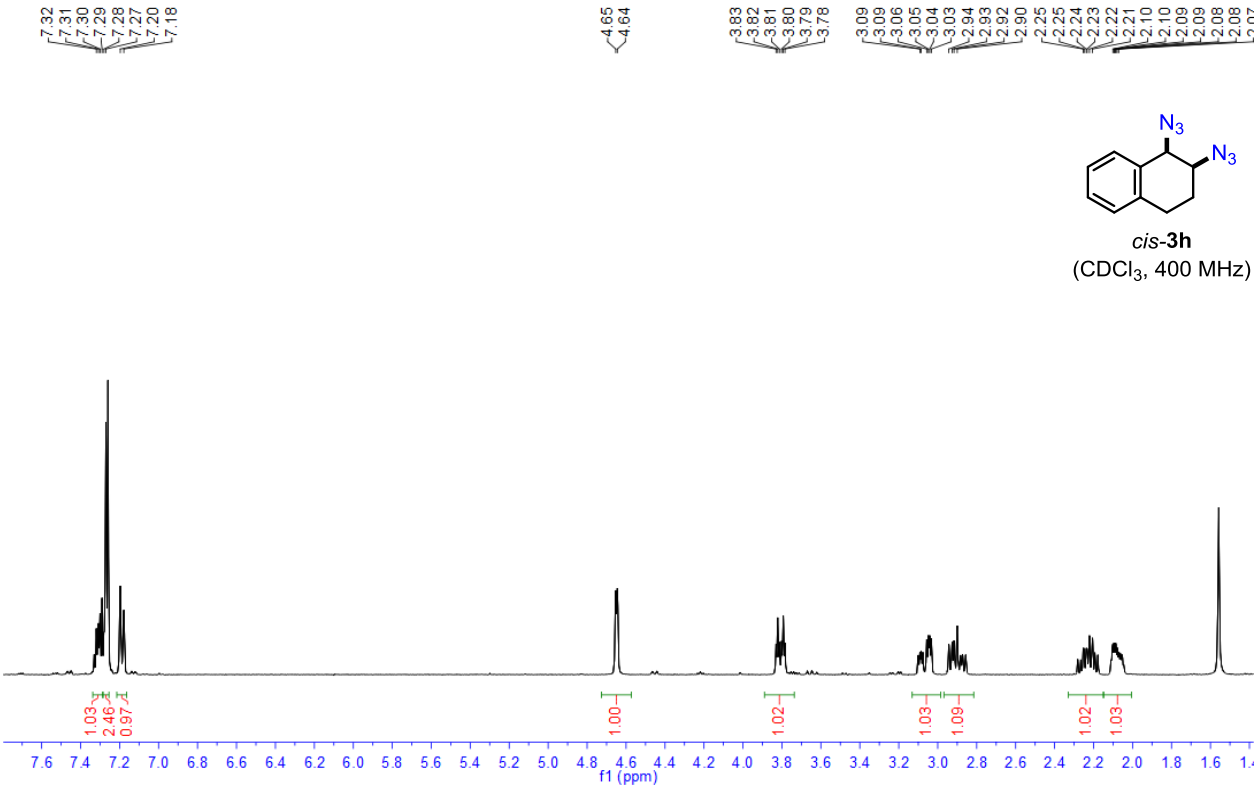
4g
(CD_3OD, 100 MHz)



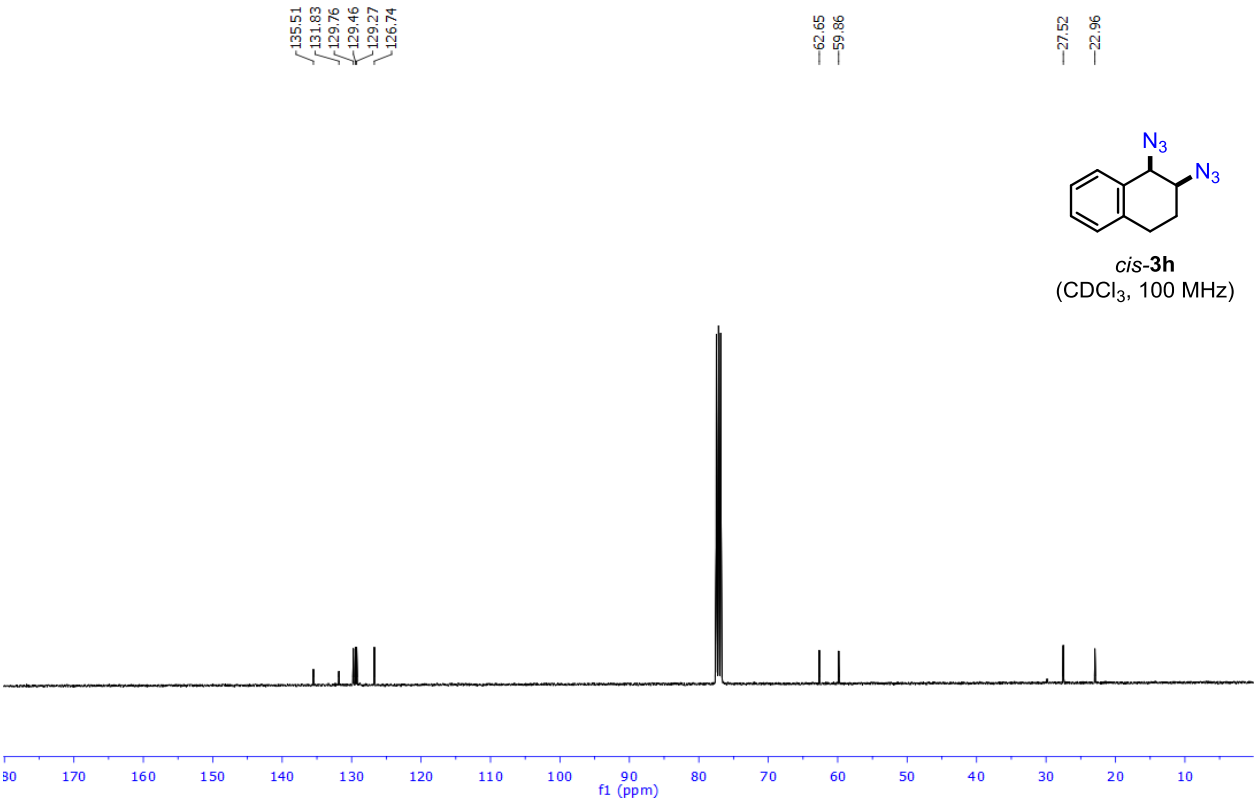
trans-**3h**
($CDCl_3$, 400 MHz)



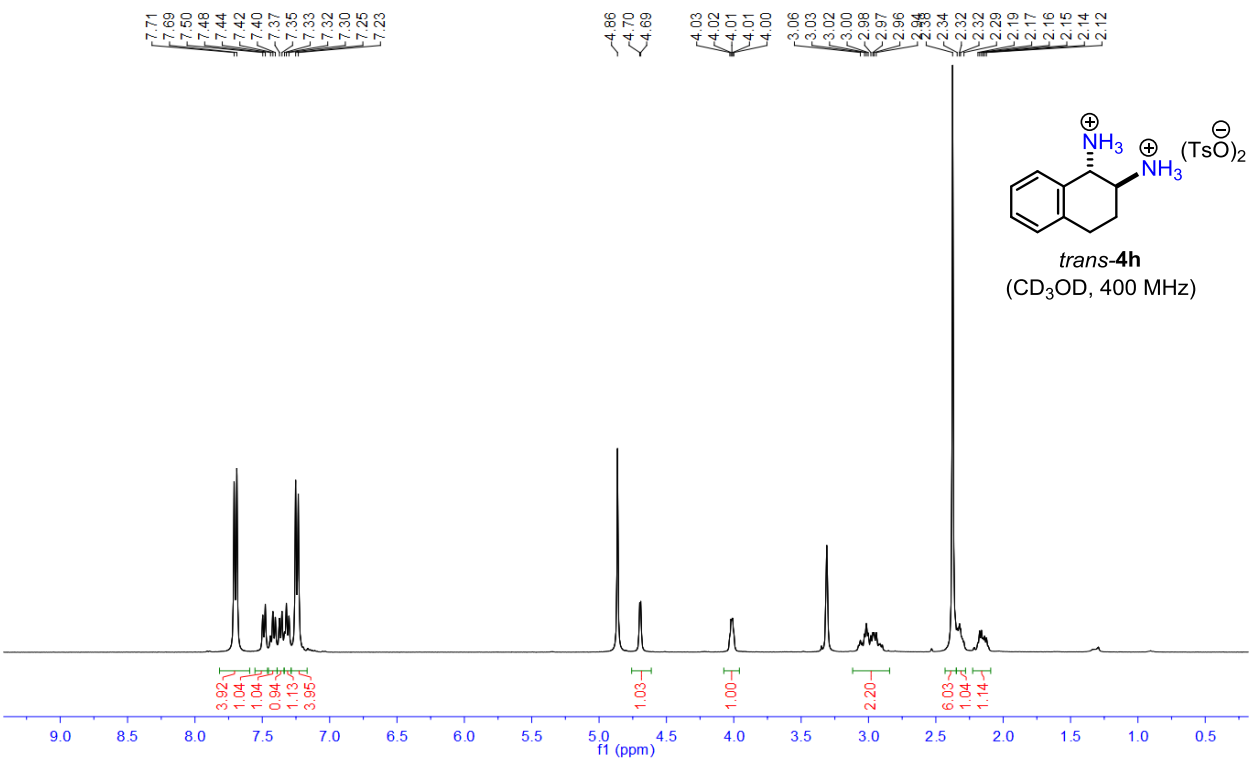
trans-**3h**
($CDCl_3$, 100 MHz)

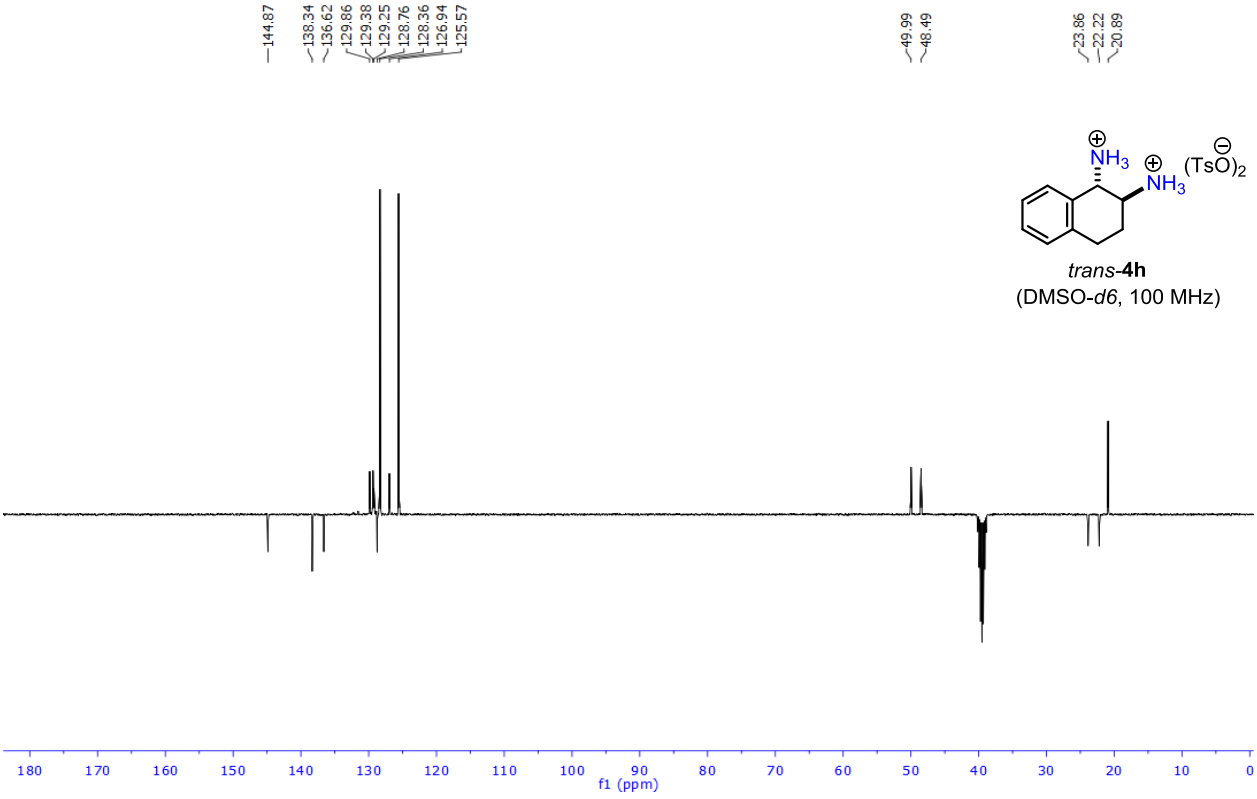


cis-**3h**
($CDCl_3$, 400 MHz)

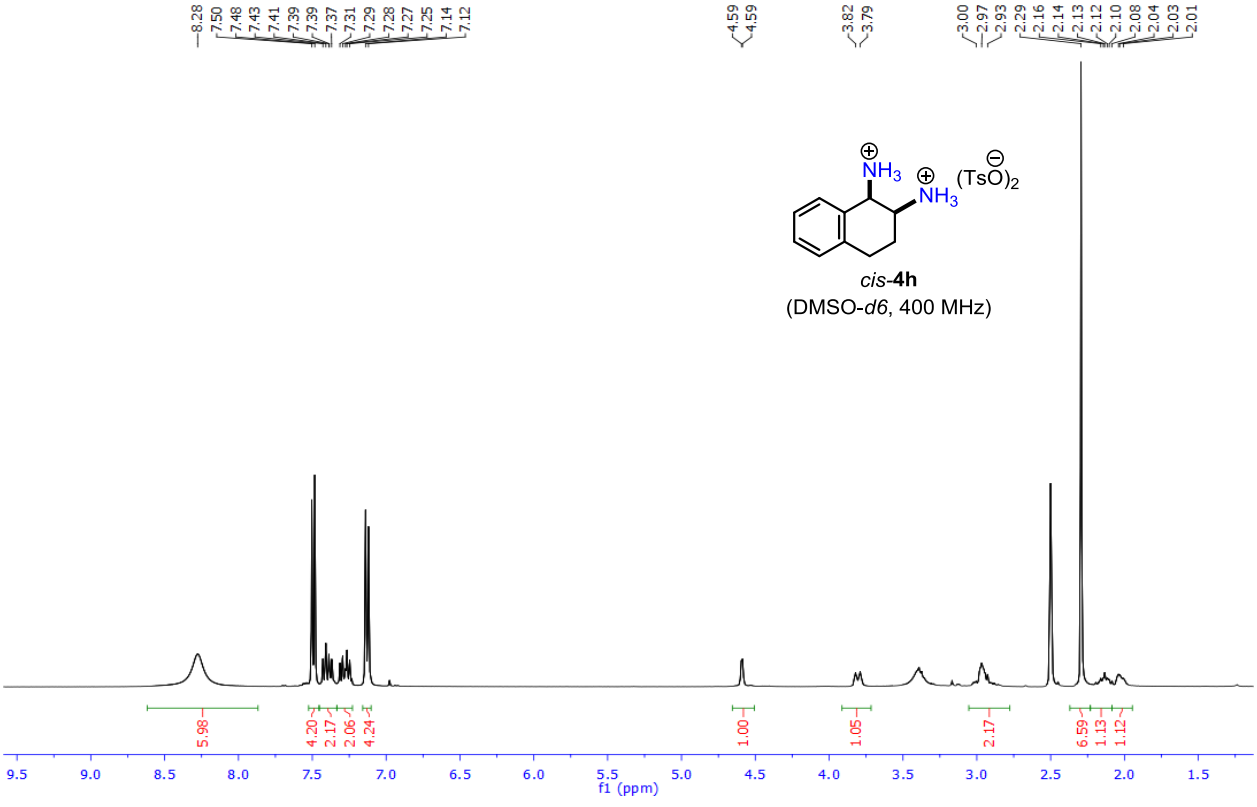


cis-**3h**
($CDCl_3$, 100 MHz)

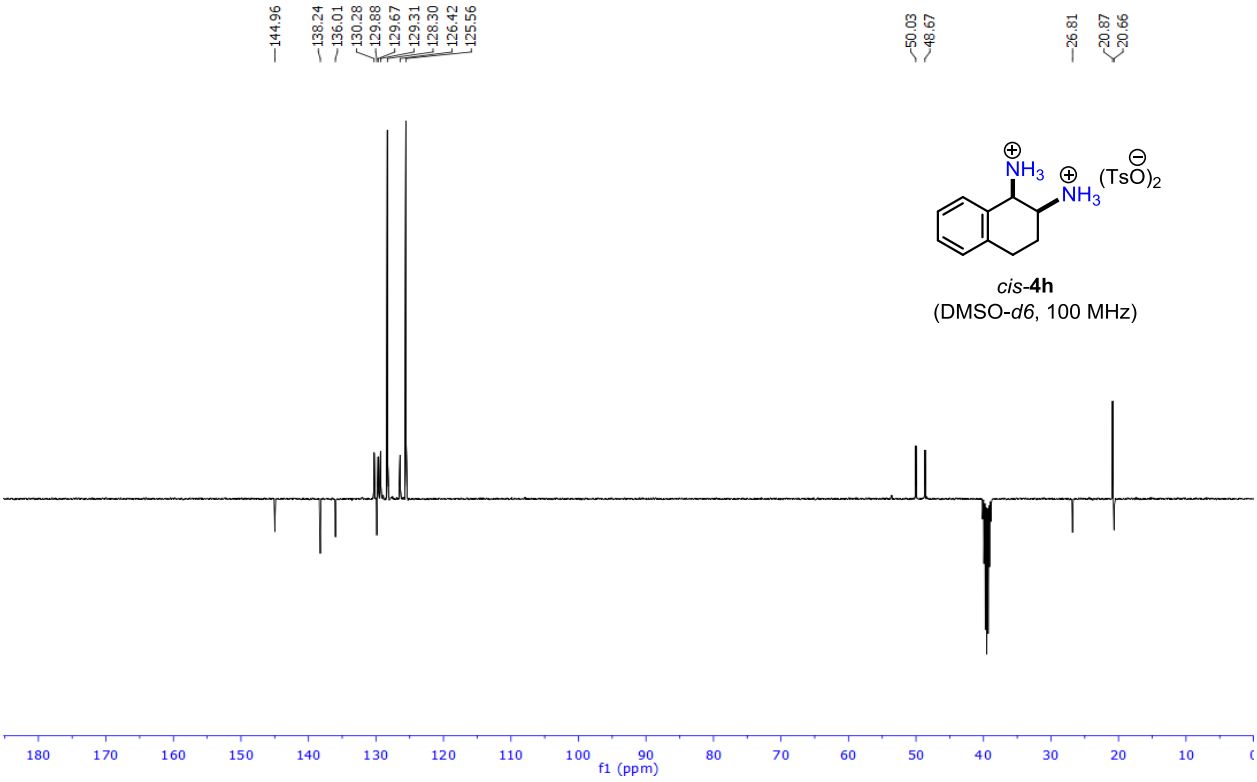

7.71
7.69
7.50
7.48
7.44
7.42
7.40
7.37
7.35
7.33
7.32
7.30
7.25
7.23
4.86
4.70
4.69
4.03
4.02
4.01
4.01
4.00
3.06
3.03
3.02
3.00
2.98
2.97
2.96
2.34
2.32
2.32
2.29
2.19
2.17
2.16
2.15
2.14
2.12
NH3
NH3
(TsO)2
trans-4h
(CD3OD, 400 MHz)
3.92
1.04
1.04
0.94
1.13
3.95
1.03
1.00
2.20
6.03
1.04
1.14
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)



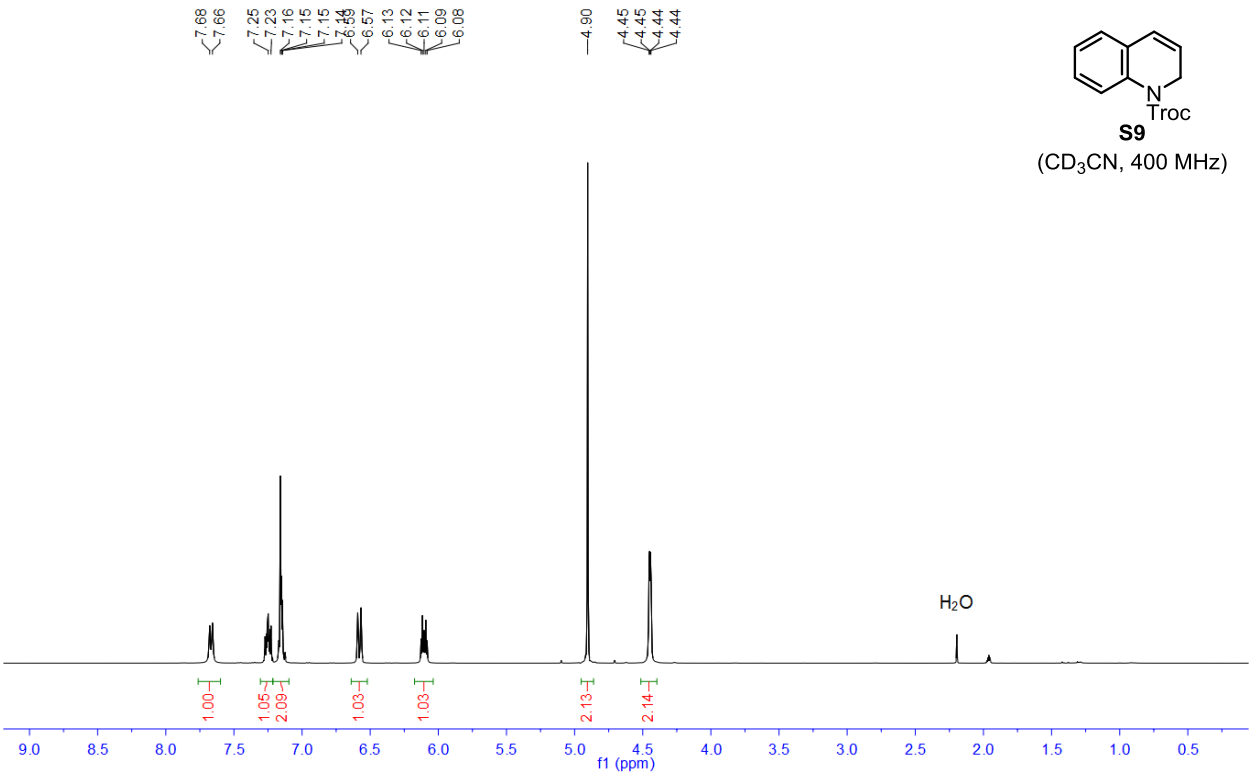
trans-**4h**
(DMSO-*d6*, 100 MHz)



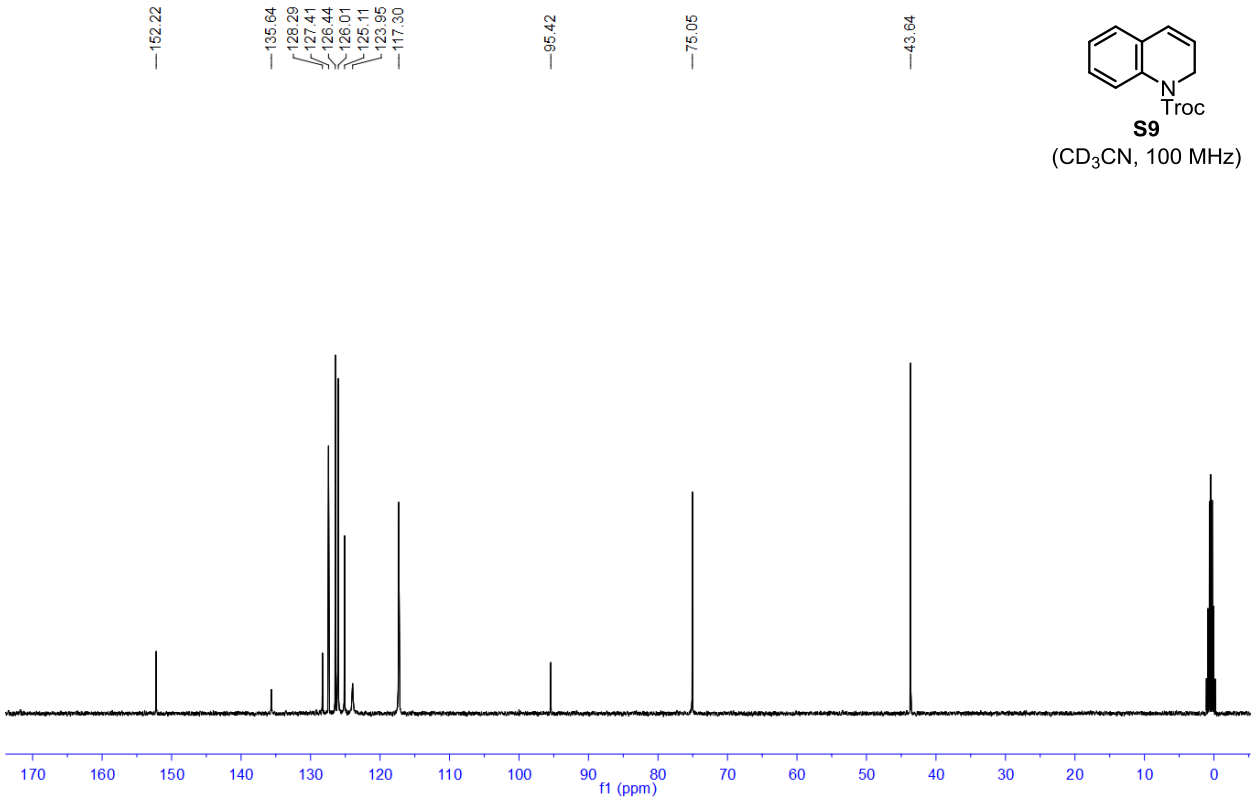
cis-**4h**
(DMSO-*d6*, 400 MHz)



cis-**4h**
(DMSO-*d6*, 100 MHz)

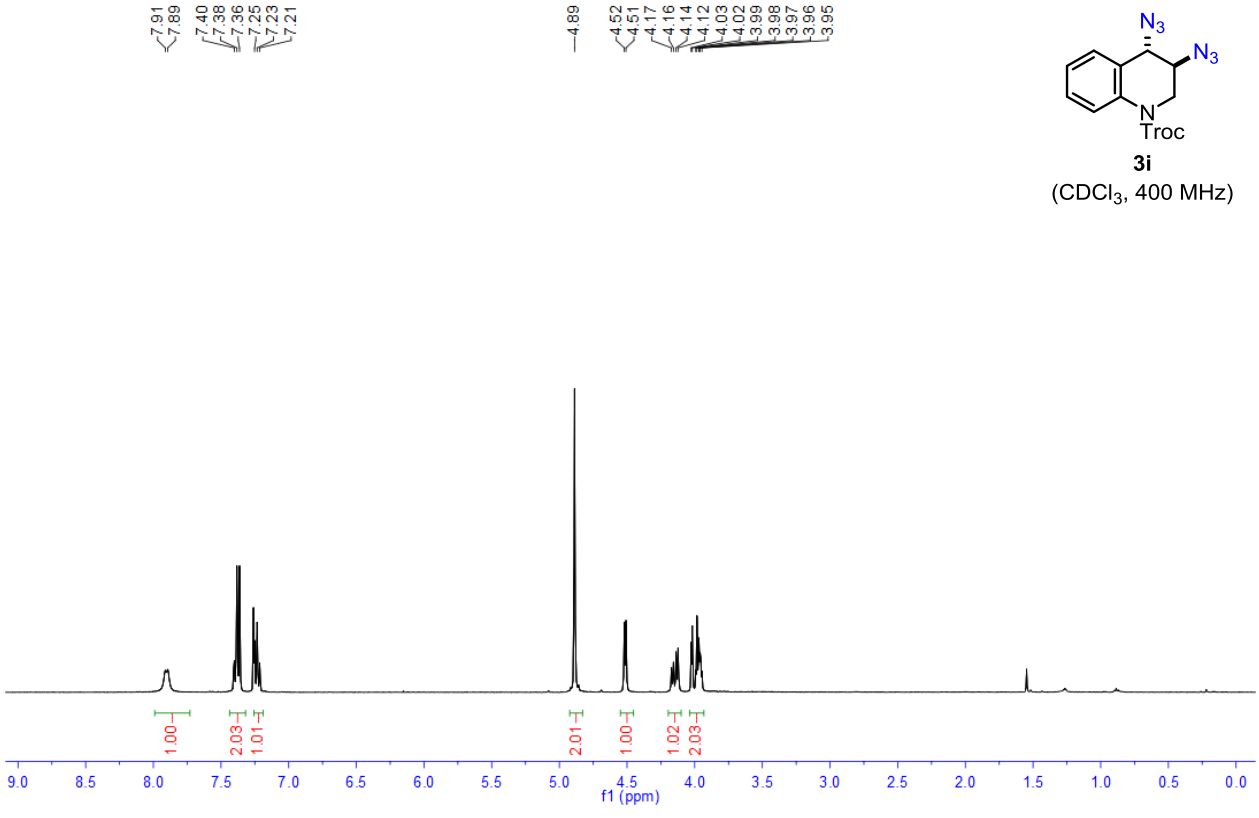


S9
(CD_3CN, 400 MHz)



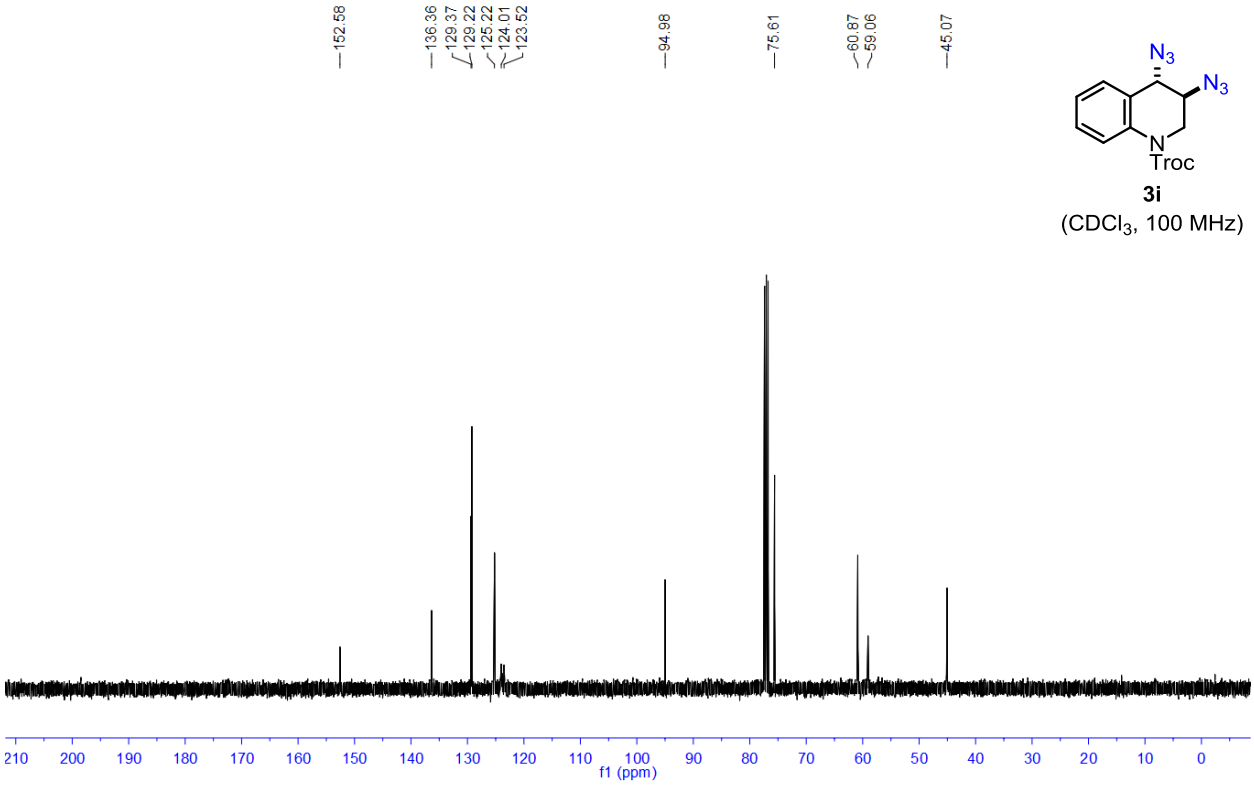
S9

(CD_3CN, 100 MHz)



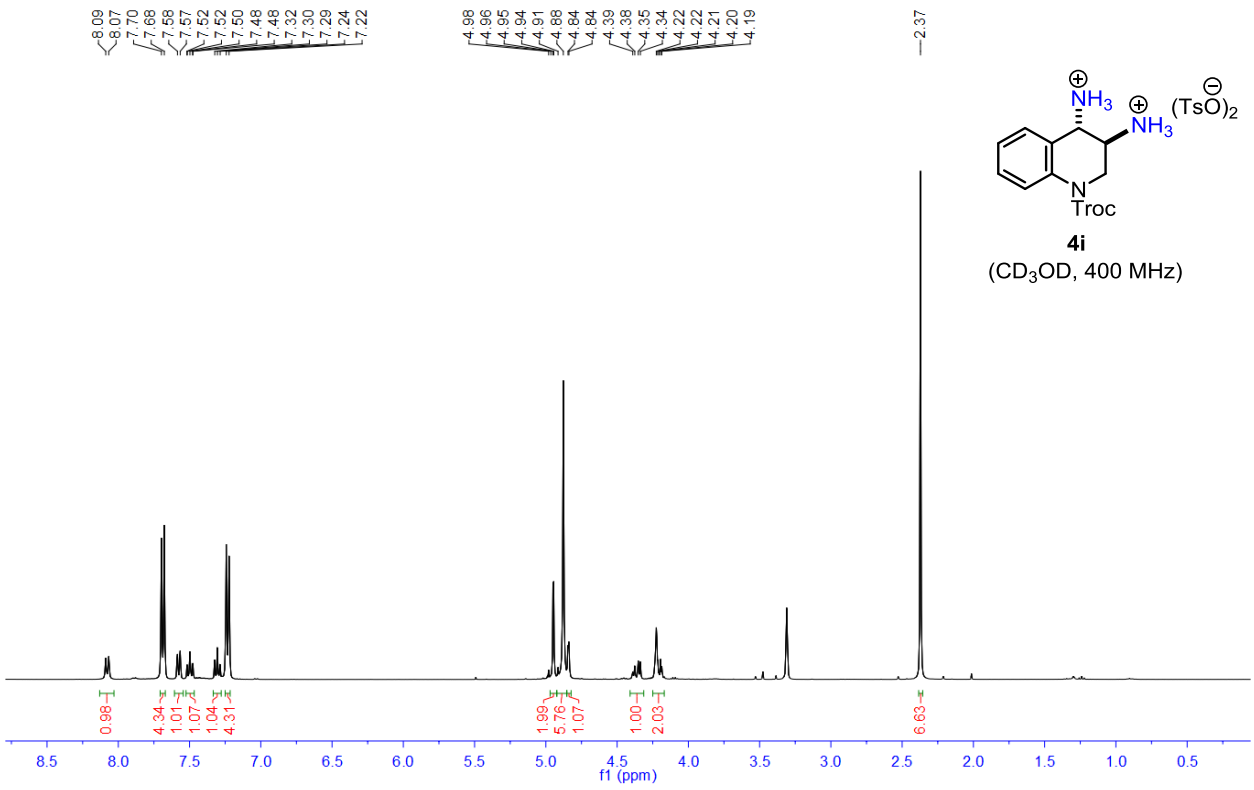
3i

($CDCl_3$, 400 MHz)



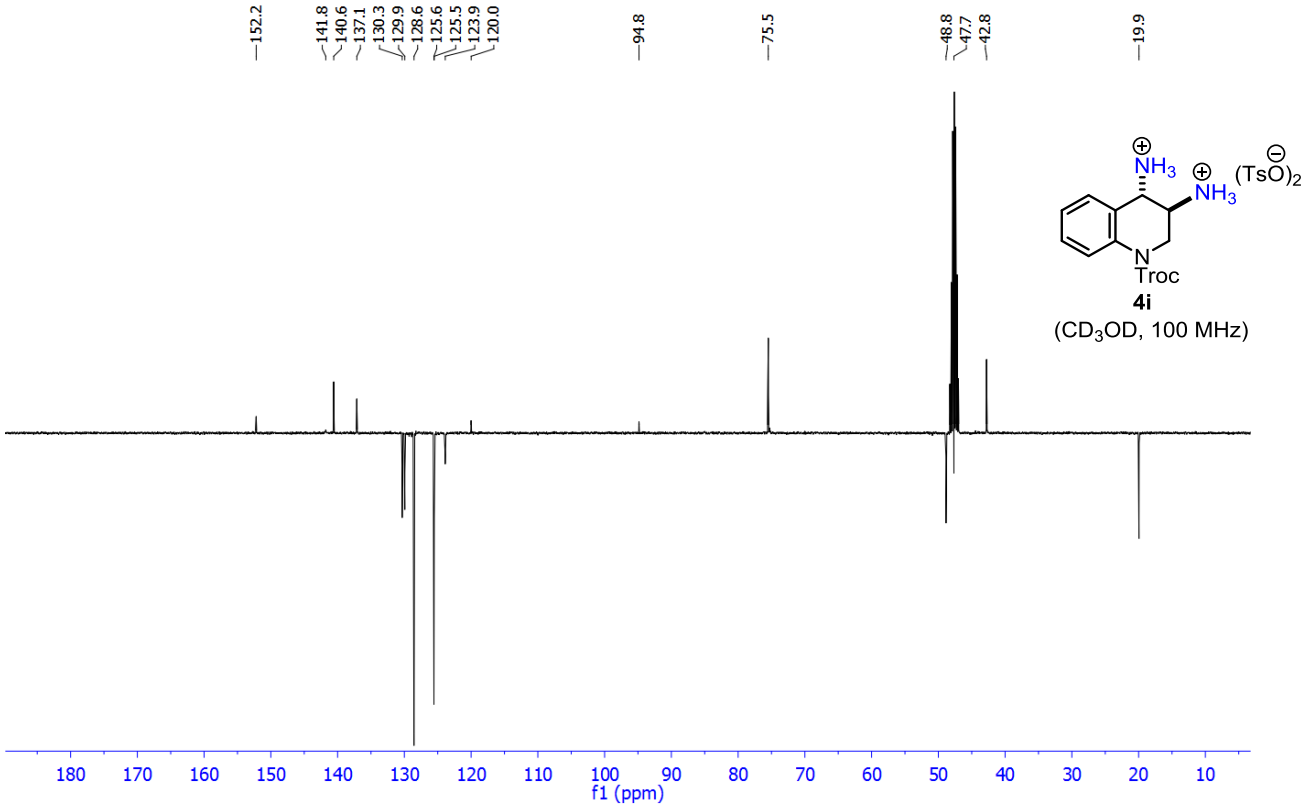
3i

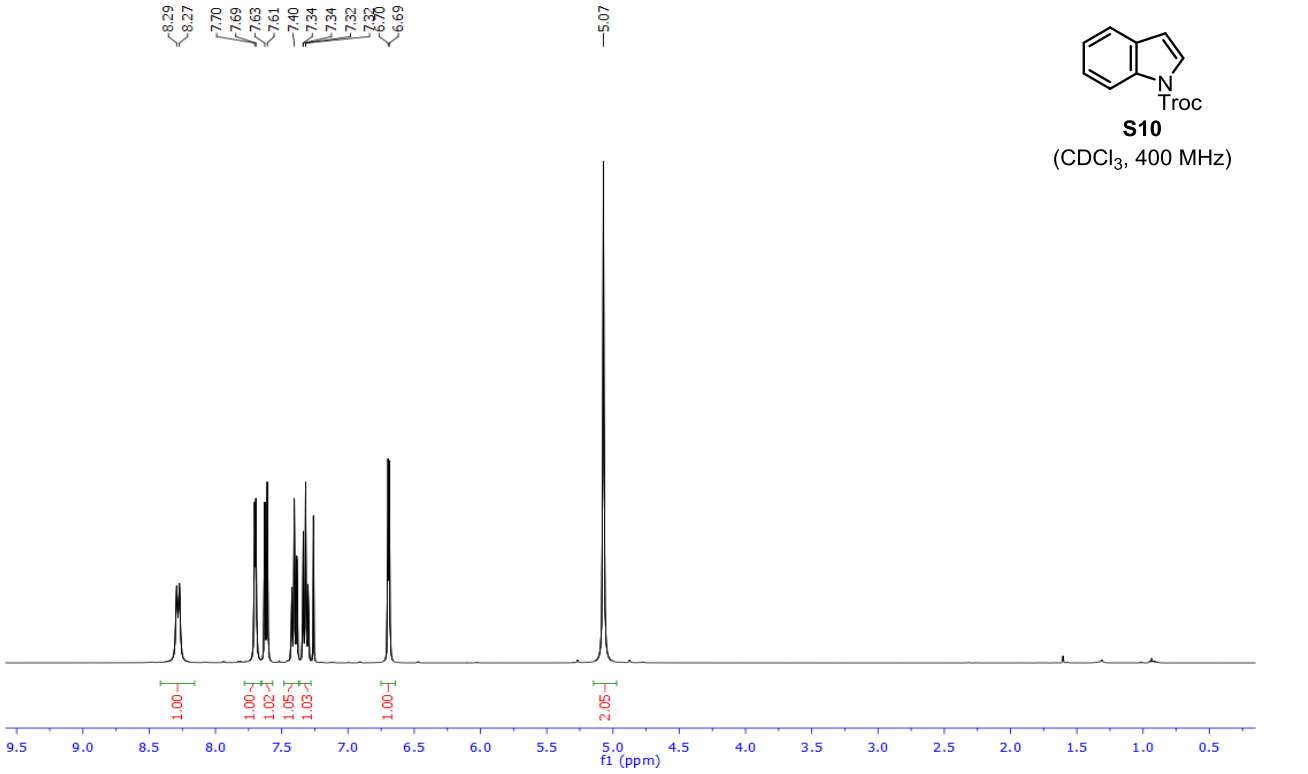
($CDCl_3$, 100 MHz)

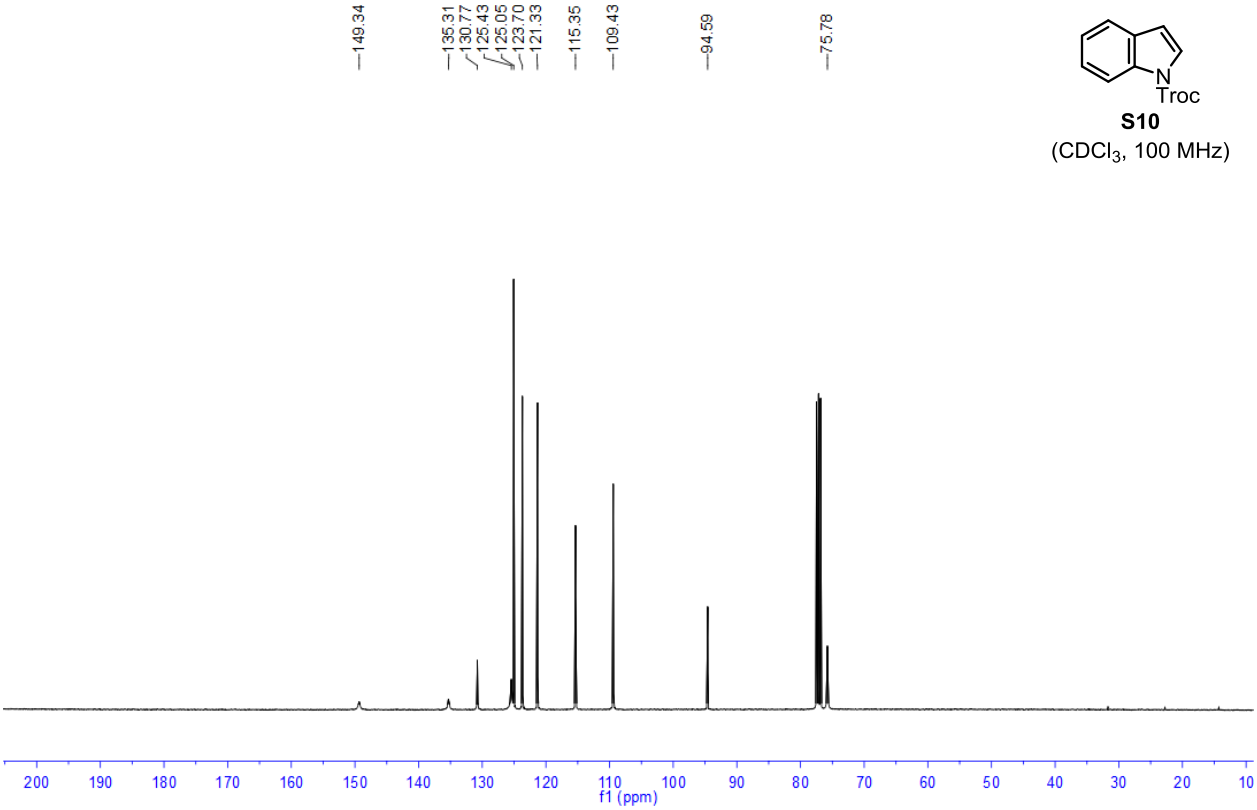


4i

(CD_3OD, 400 MHz)

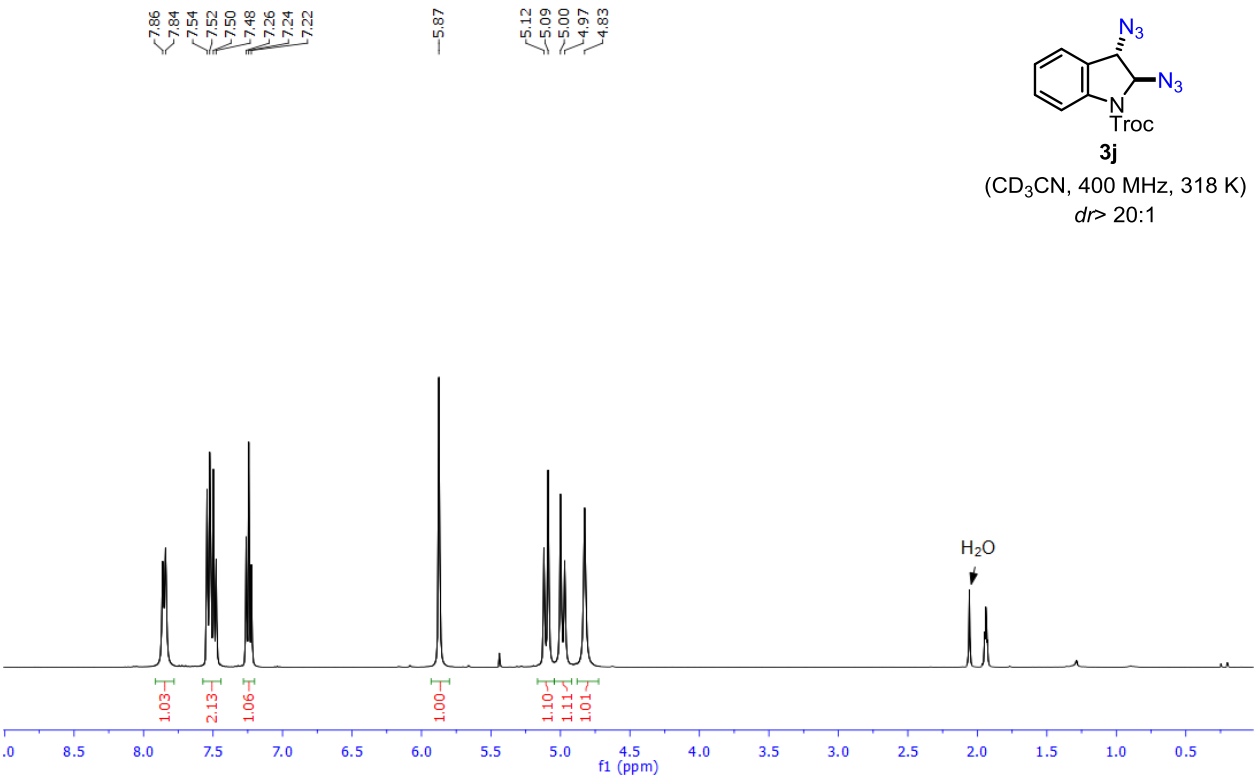

152.2
141.8
140.6
137.1
130.3
129.9
128.6
125.6
125.5
123.9
120.0
94.8
75.5
48.8
47.7
42.8
19.9
NH3
NH3
(TsO)2
N
Troc
4i
(CD3OD, 100 MHz)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


8.29
8.27
7.70
7.69
7.63
7.61
7.40
7.34
7.34
7.32
7.32
6.70
6.69
5.07
N
Troc
S10
(CDCl3, 400 MHz)
1.00
1.00
1.02
1.05
1.03
1.00
2.05
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)



S10

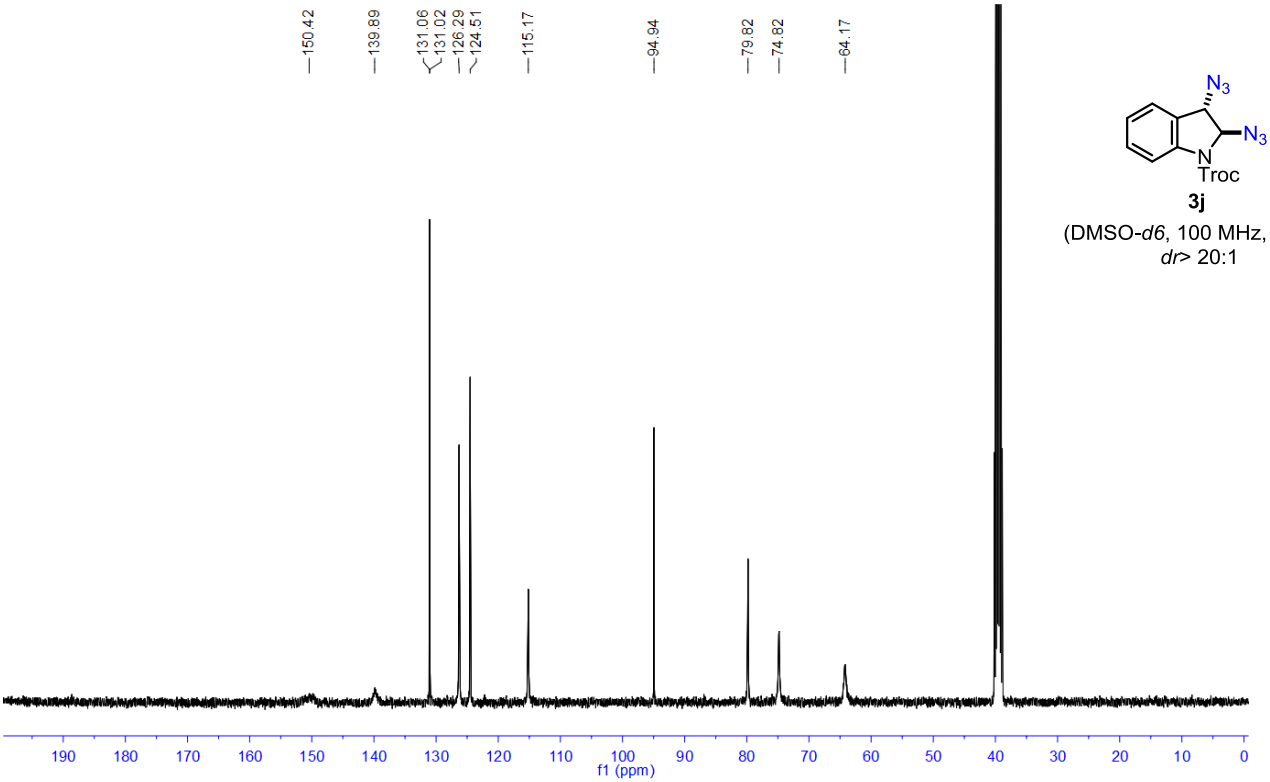
($CDCl_3$, 100 MHz)



3j

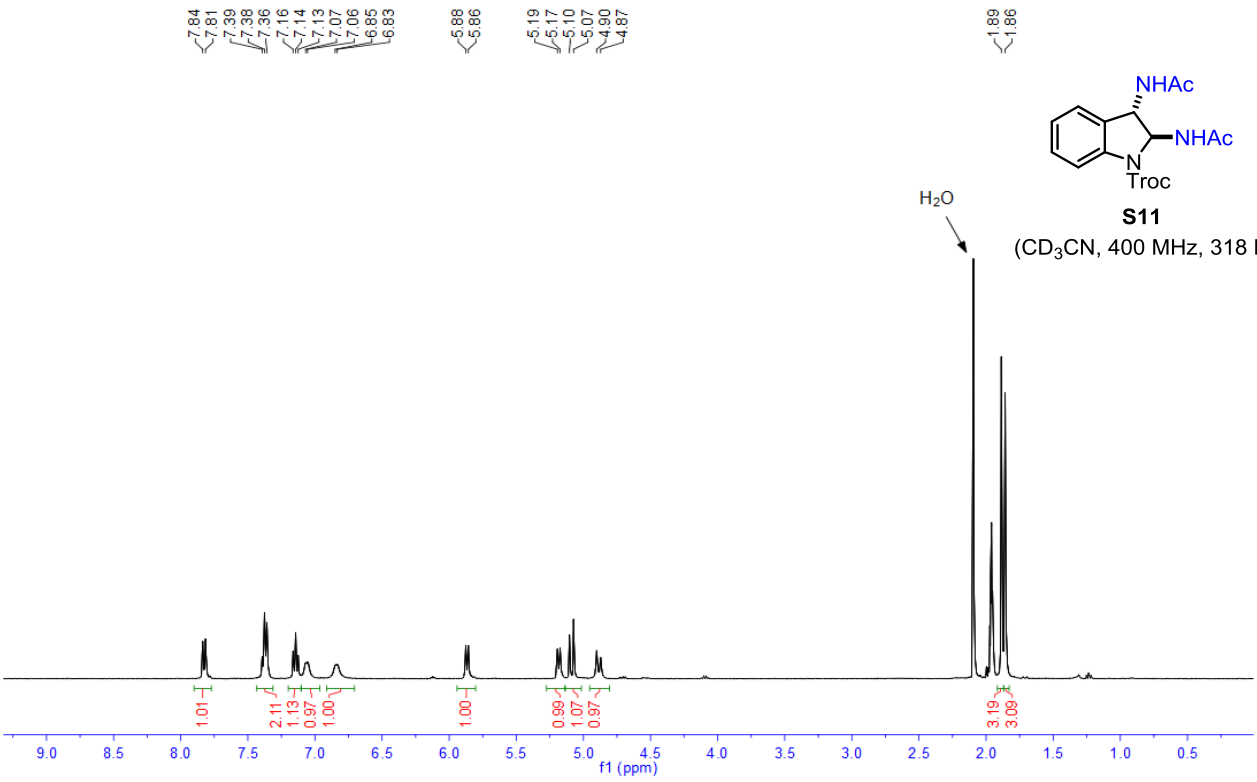
(CD_3CN, 400 MHz, 318 K)

dr> 20:1



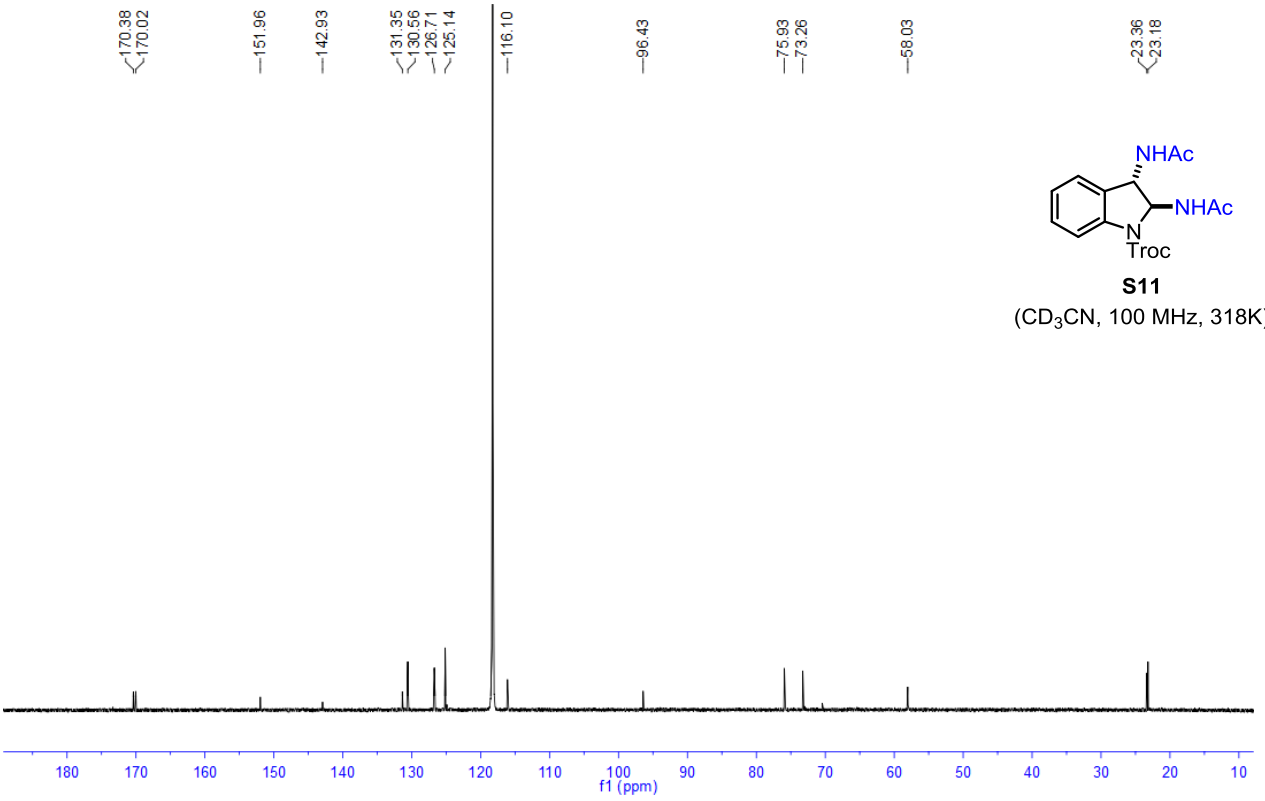
3j

(DMSO-*d6*, 100 MHz, 318 K)
dr> 20:1



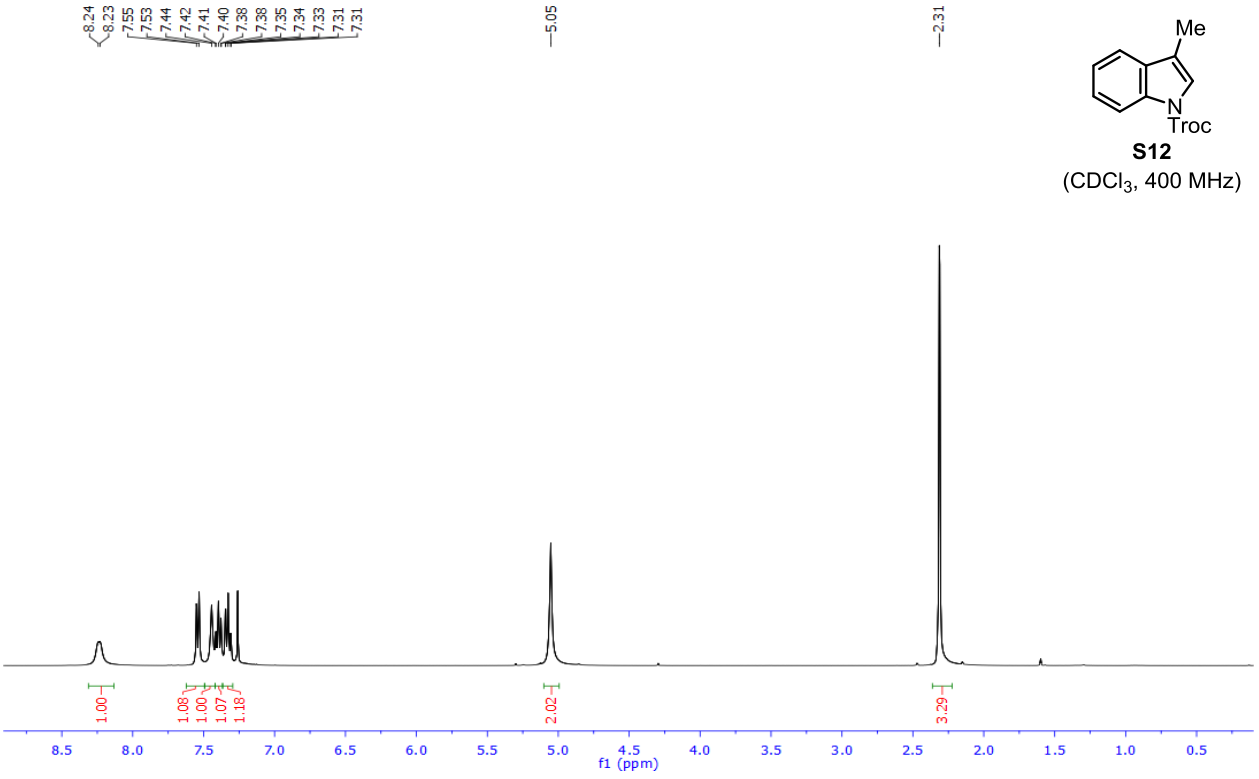
S11

(CD_3CN, 400 MHz, 318 K)



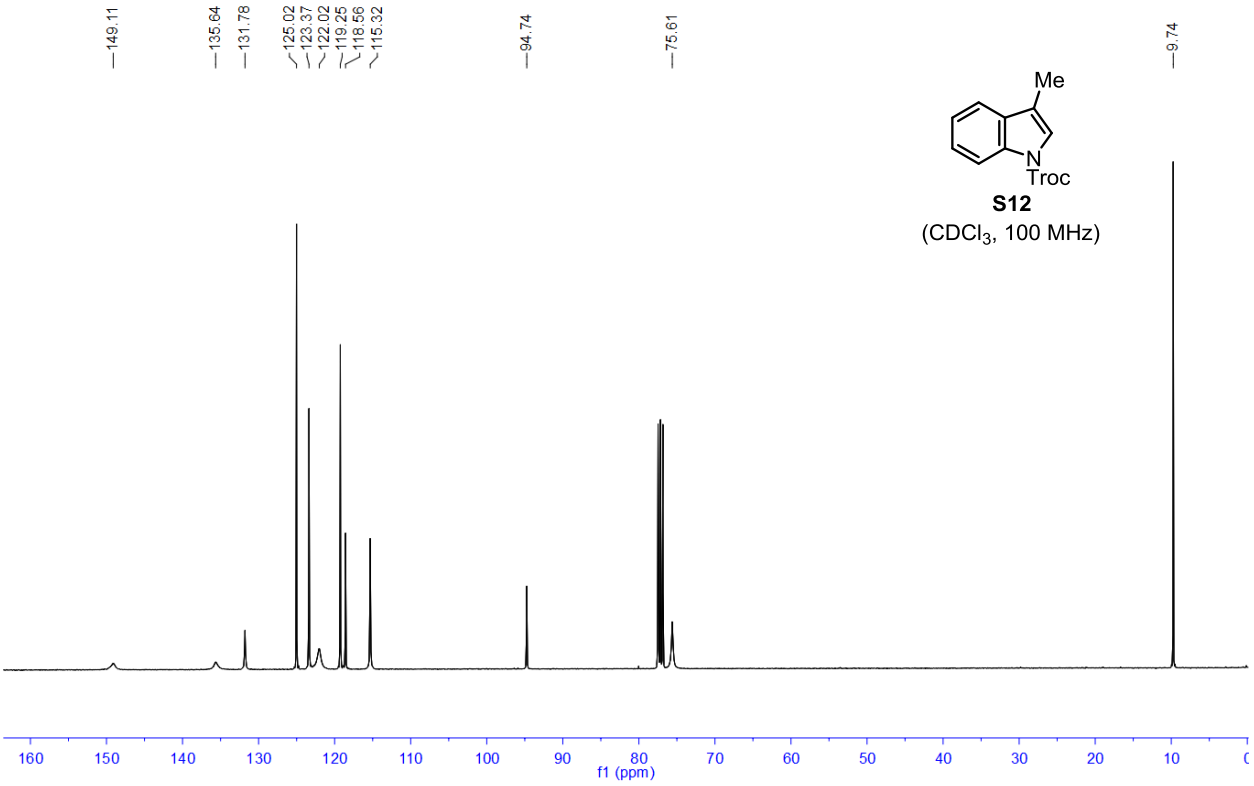
S11

(CD_3CN, 100 MHz, 318K)



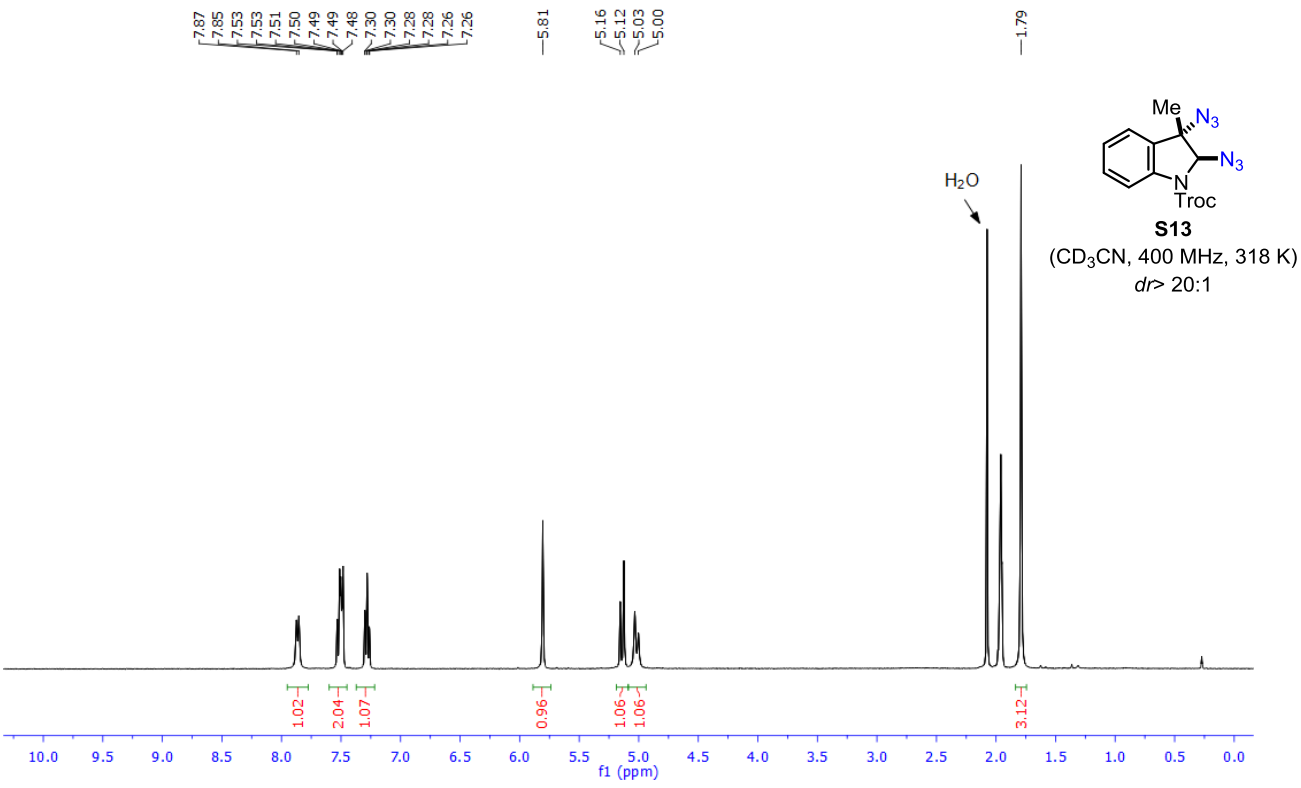
S12

($CDCl_3$, 400 MHz)



S12

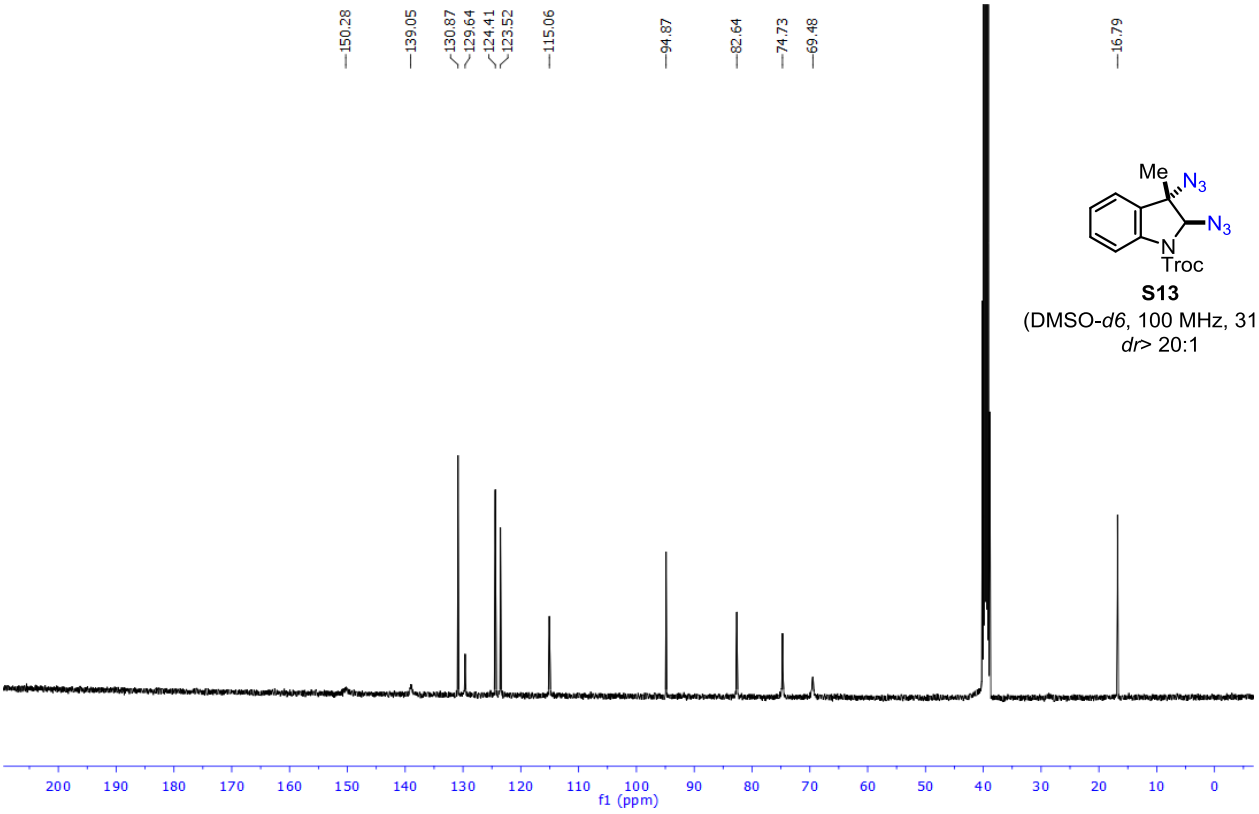
($CDCl_3$, 100 MHz)



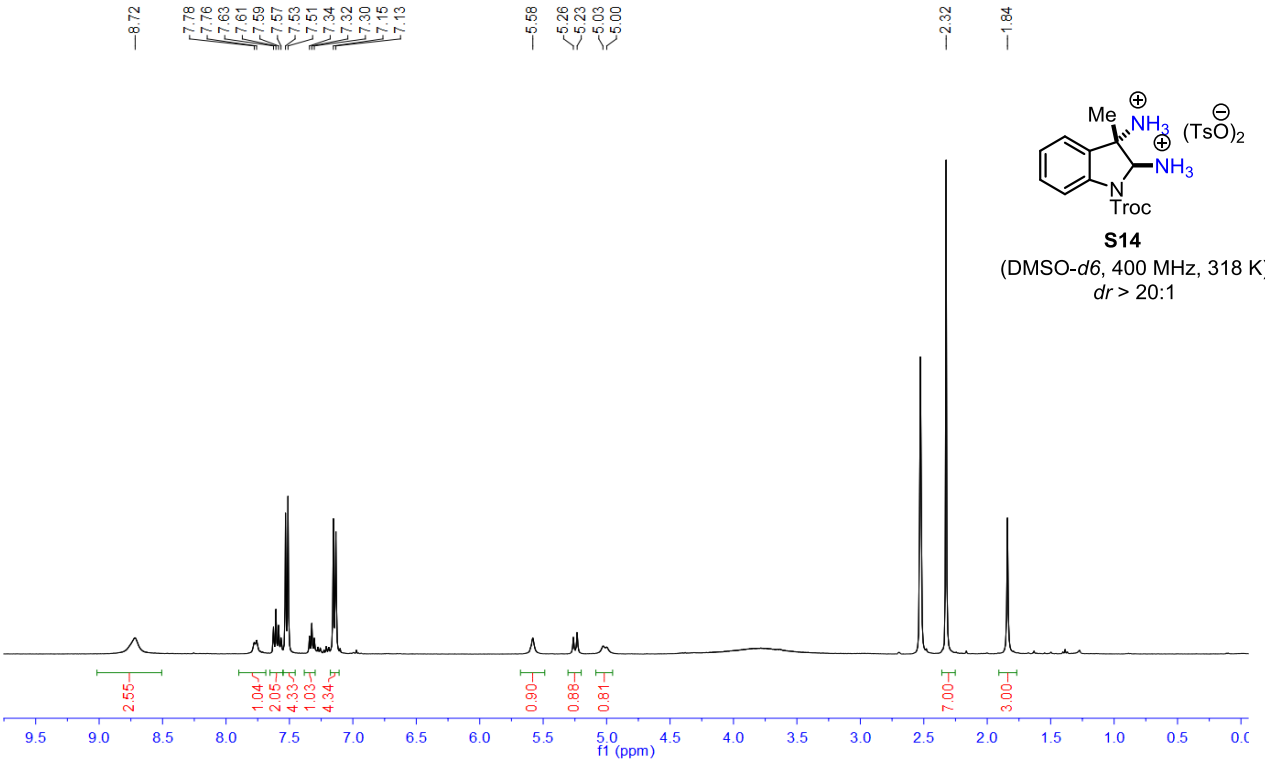
S13

(CD_3CN, 400 MHz, 318 K)

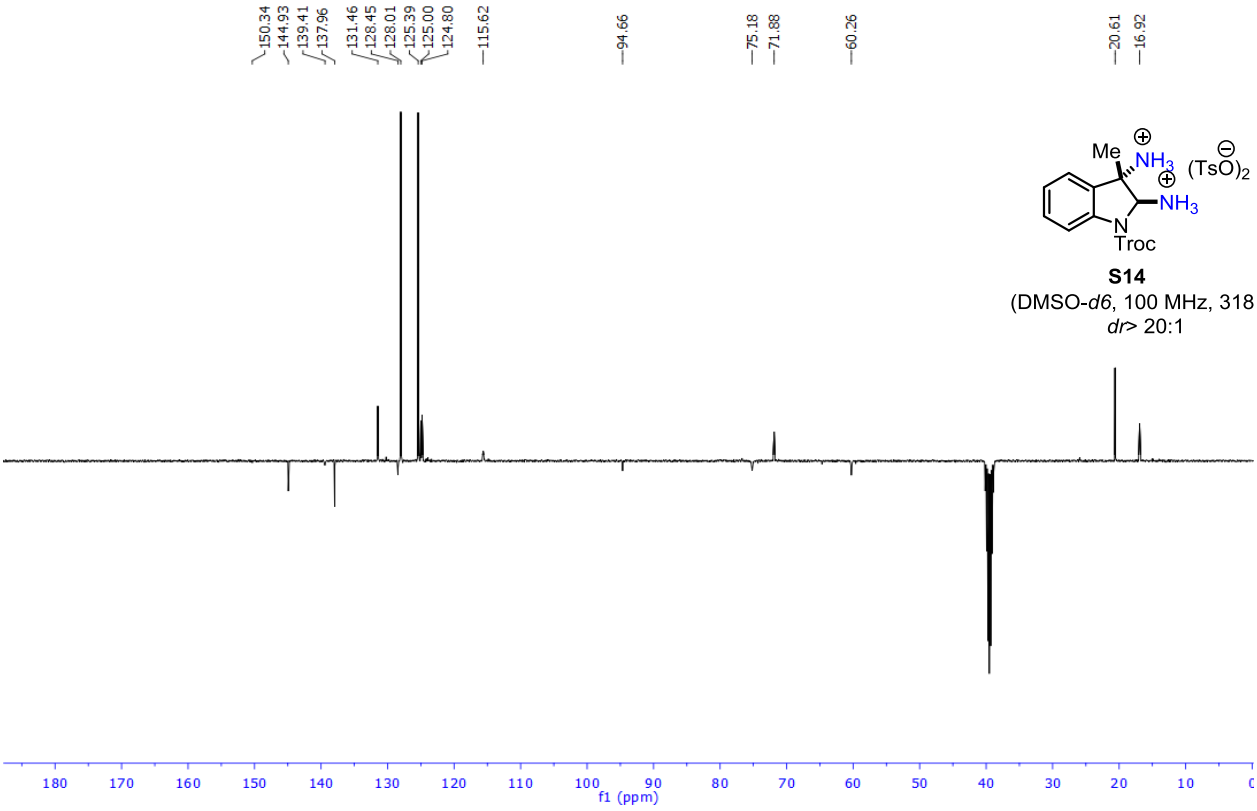
dr> 20:1



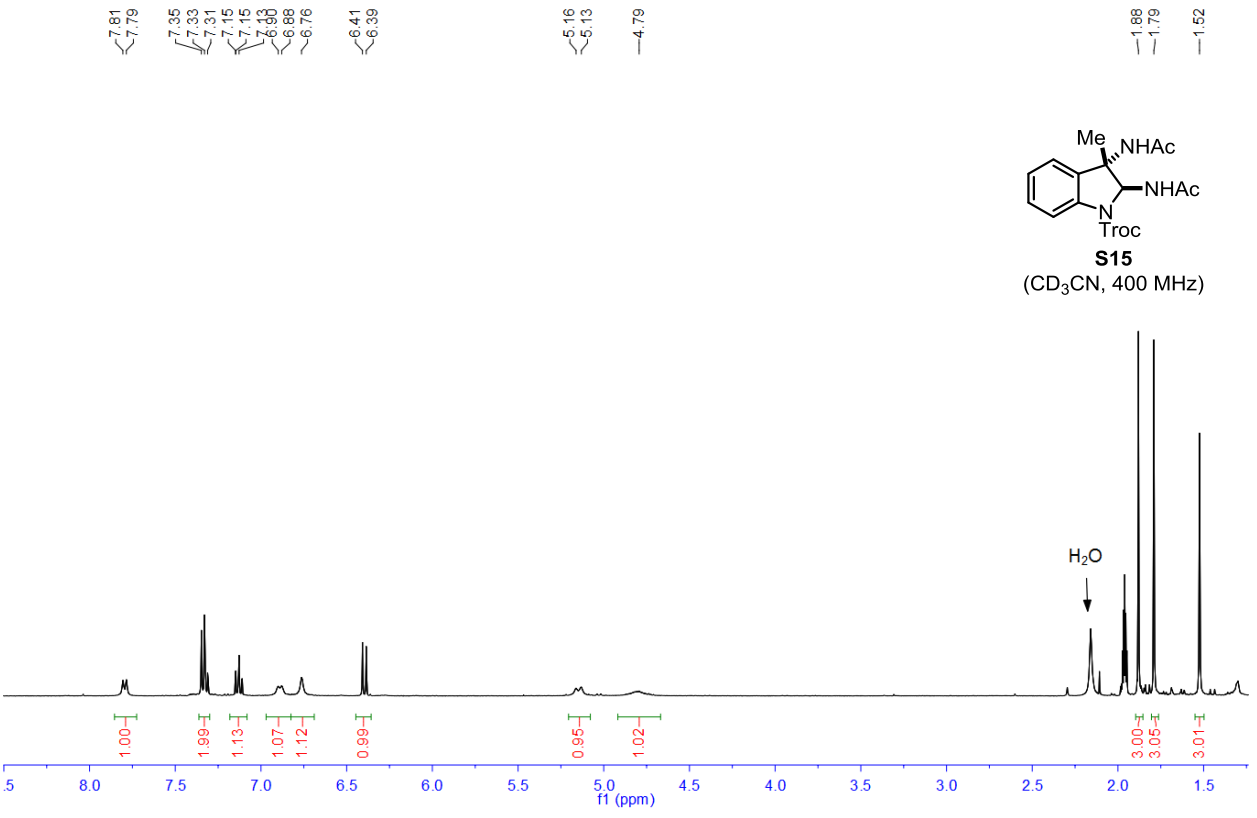
S13
(DMSO-*d6*, 100 MHz, 318 K)
dr> 20:1



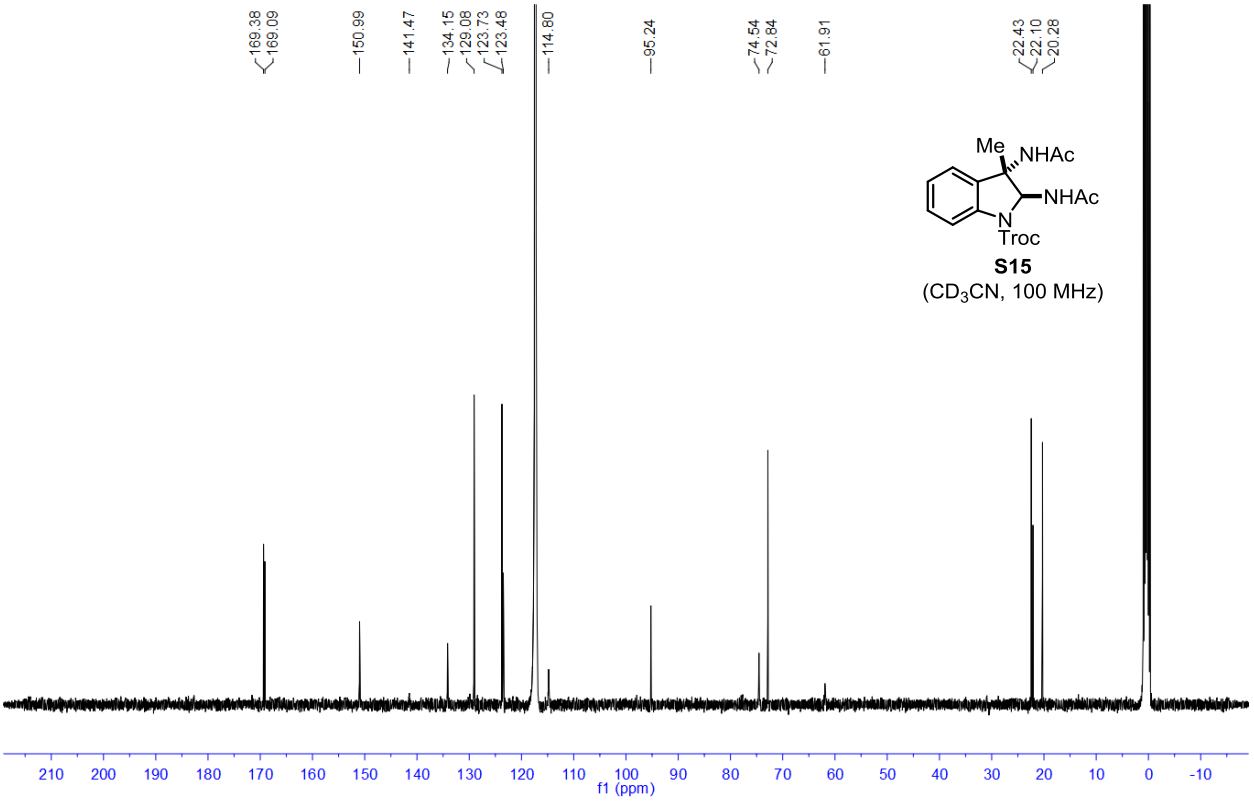
S14
(DMSO-*d6*, 400 MHz, 318 K)
dr > 20:1



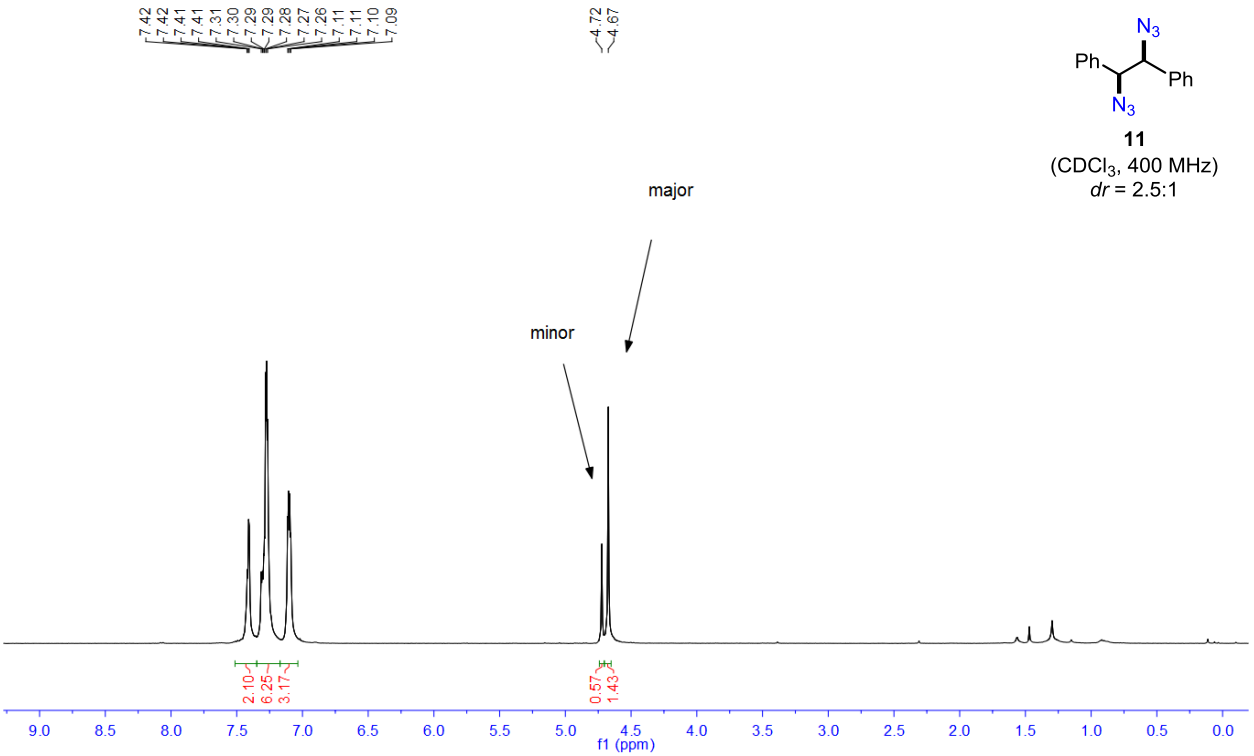
S14
(DMSO-*d6*, 100 MHz, 318 K)
dr> 20:1



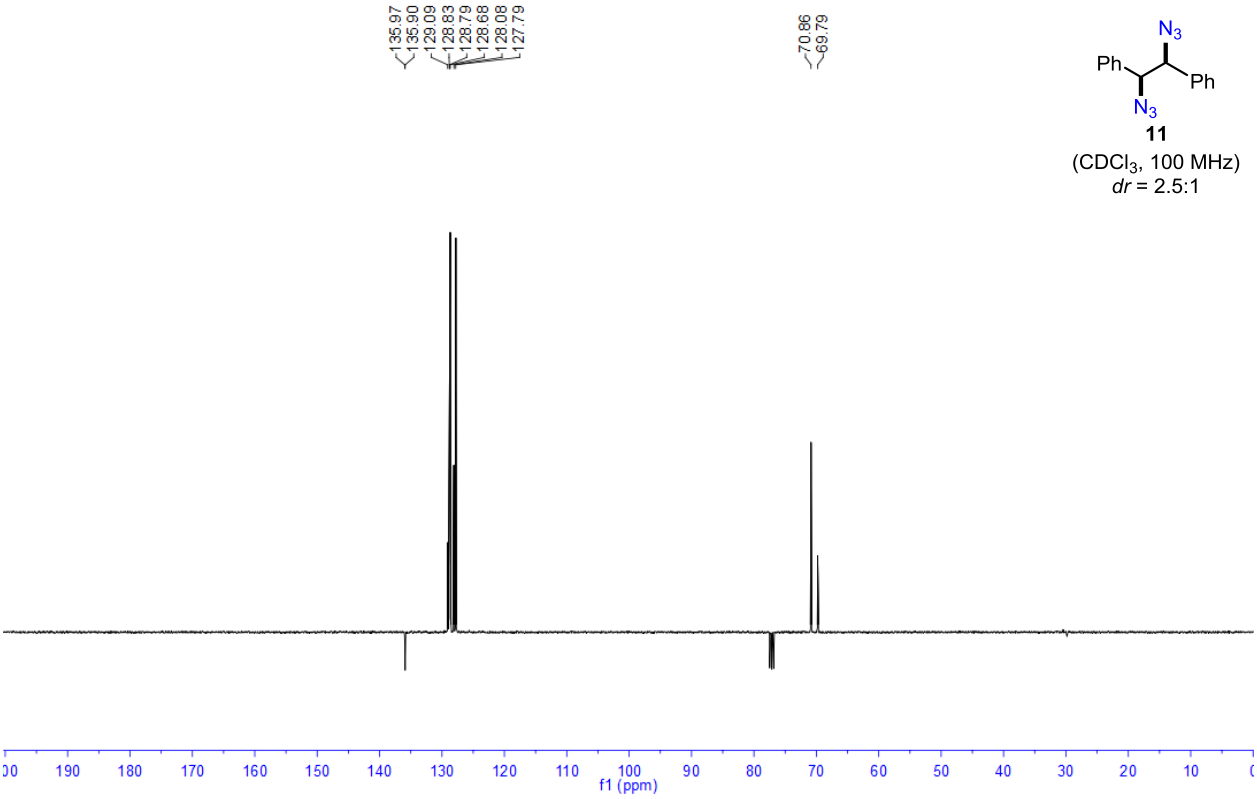
S15
(CD_3CN, 400 MHz)



S15
(CD_3CN, 100 MHz)



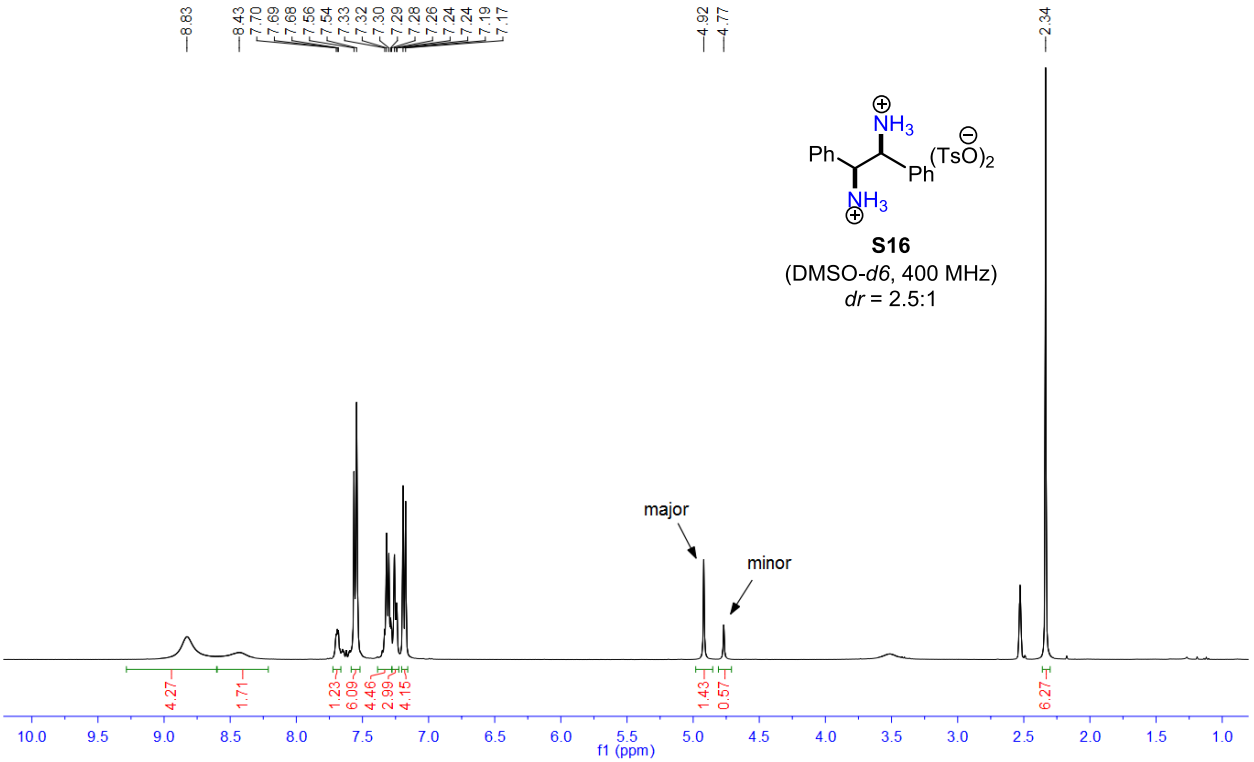
11
($CDCl_3$, 400 MHz)
dr = 2.5:1



11

($CDCl_3$, 100 MHz)

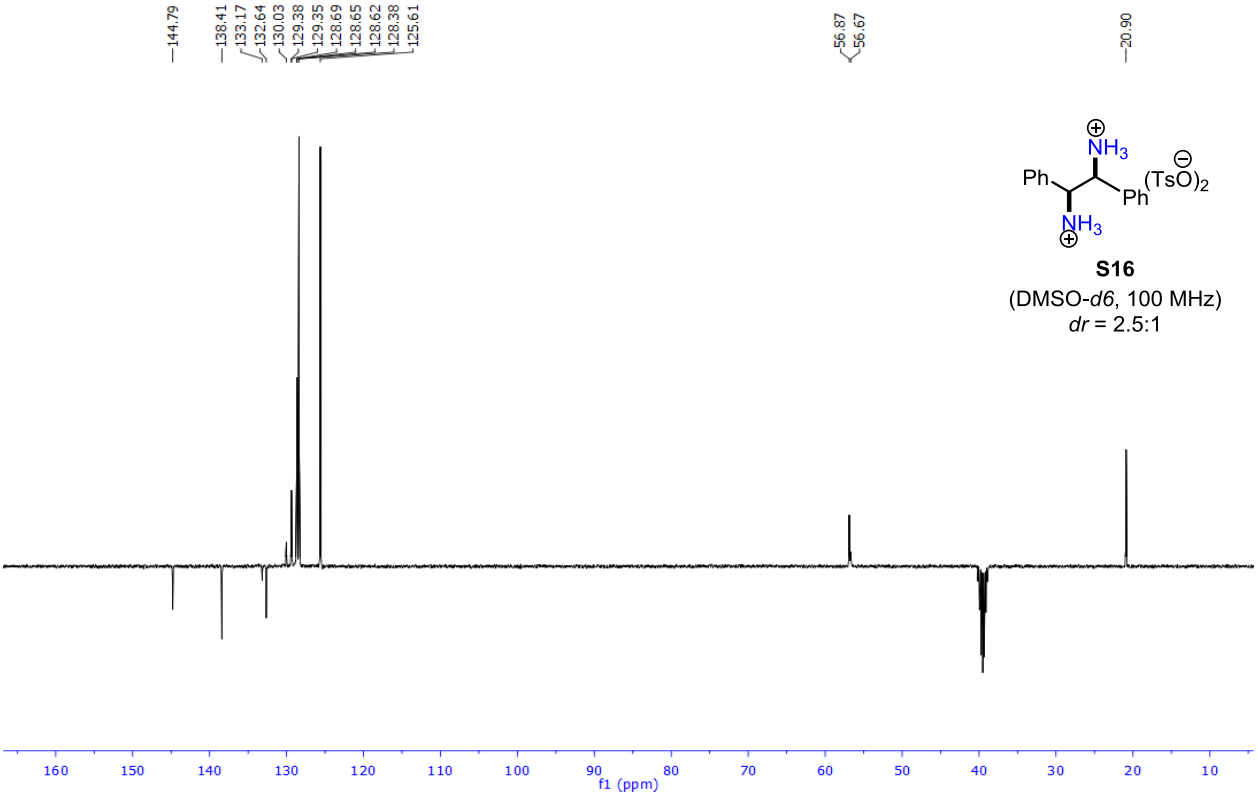
dr = 2.5:1



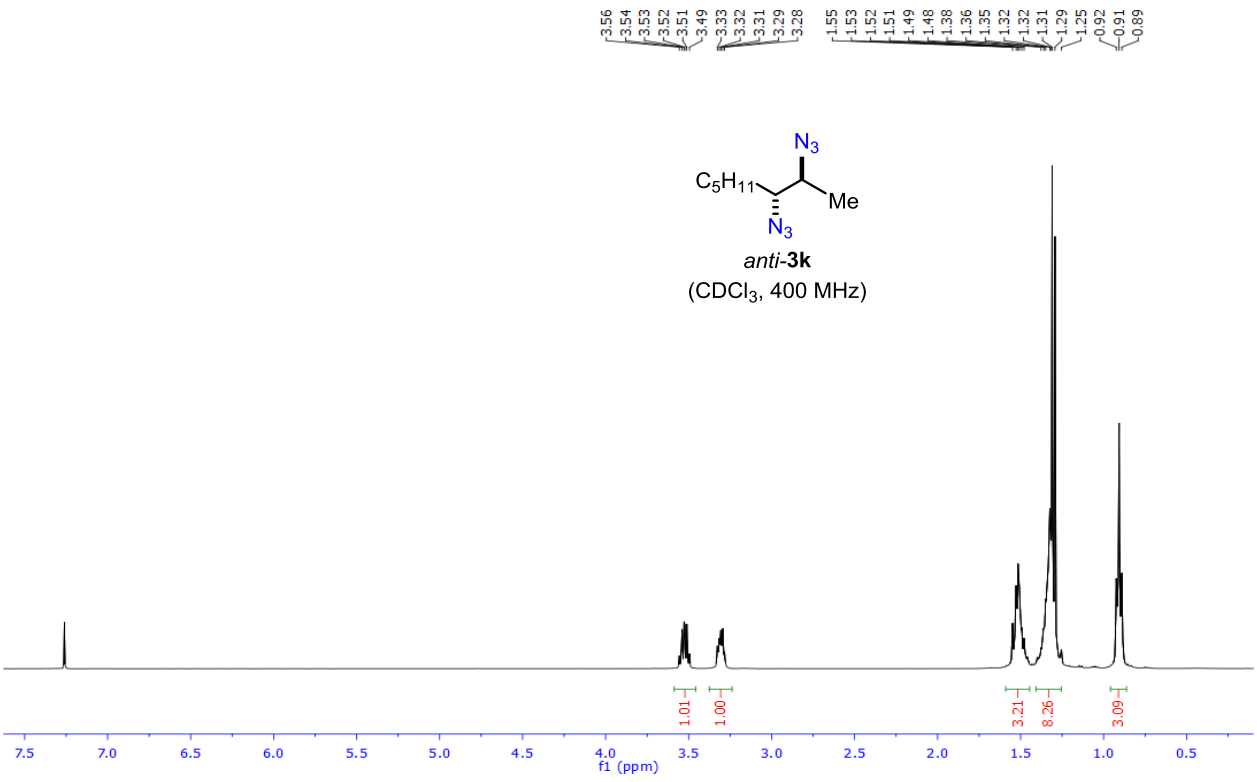
S16

(DMSO-*d6*, 400 MHz)

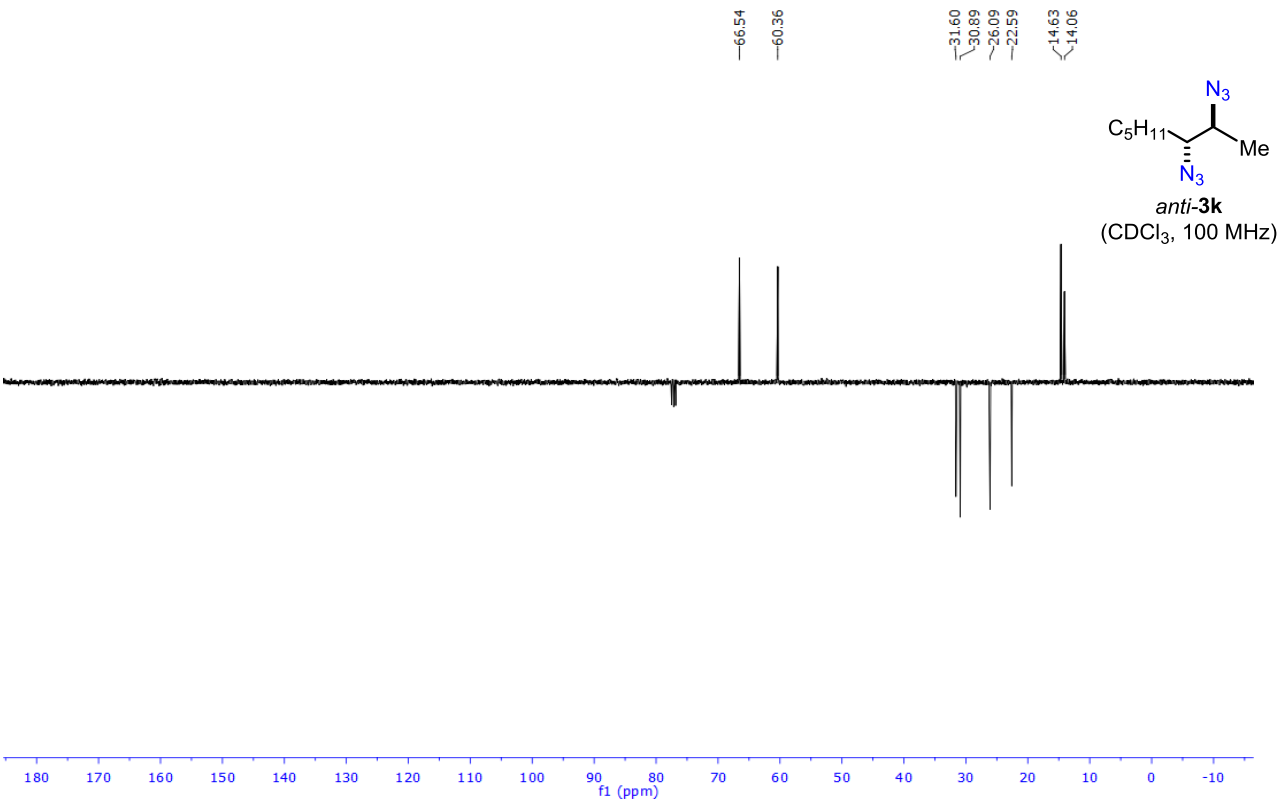
dr = 2.5:1

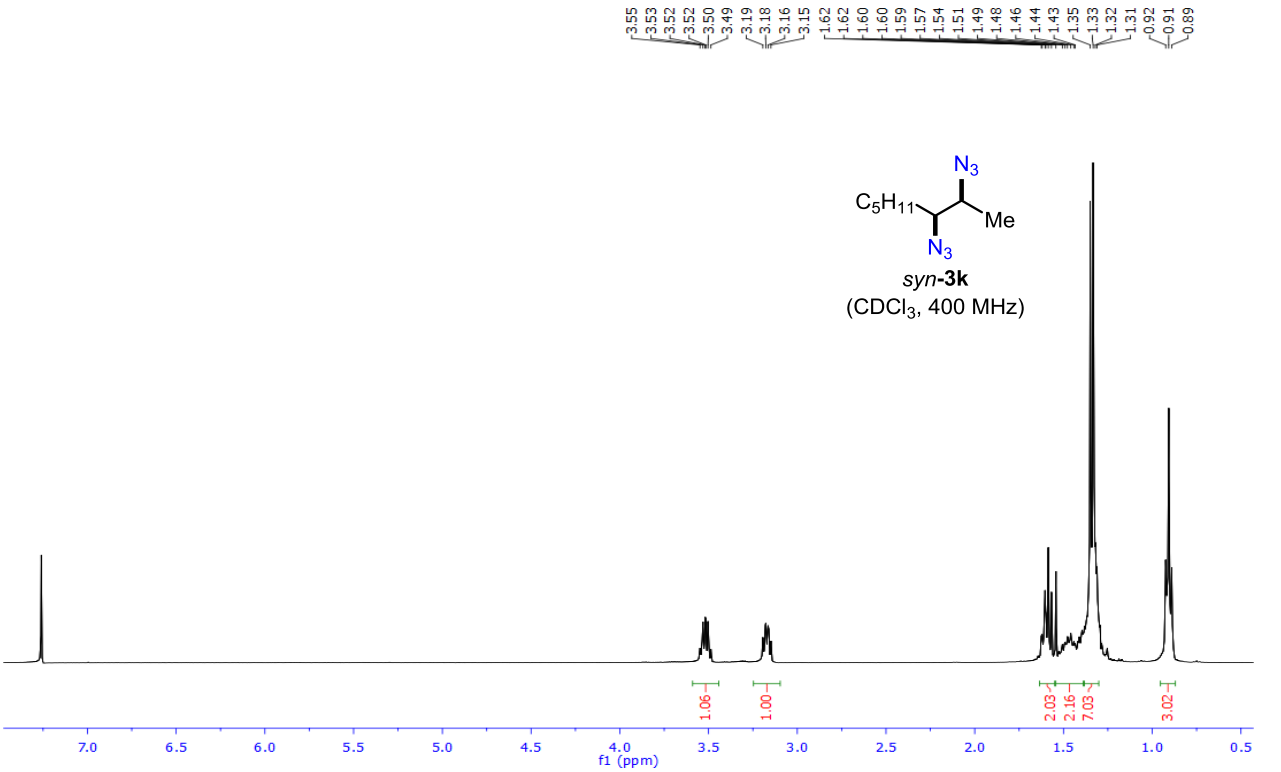


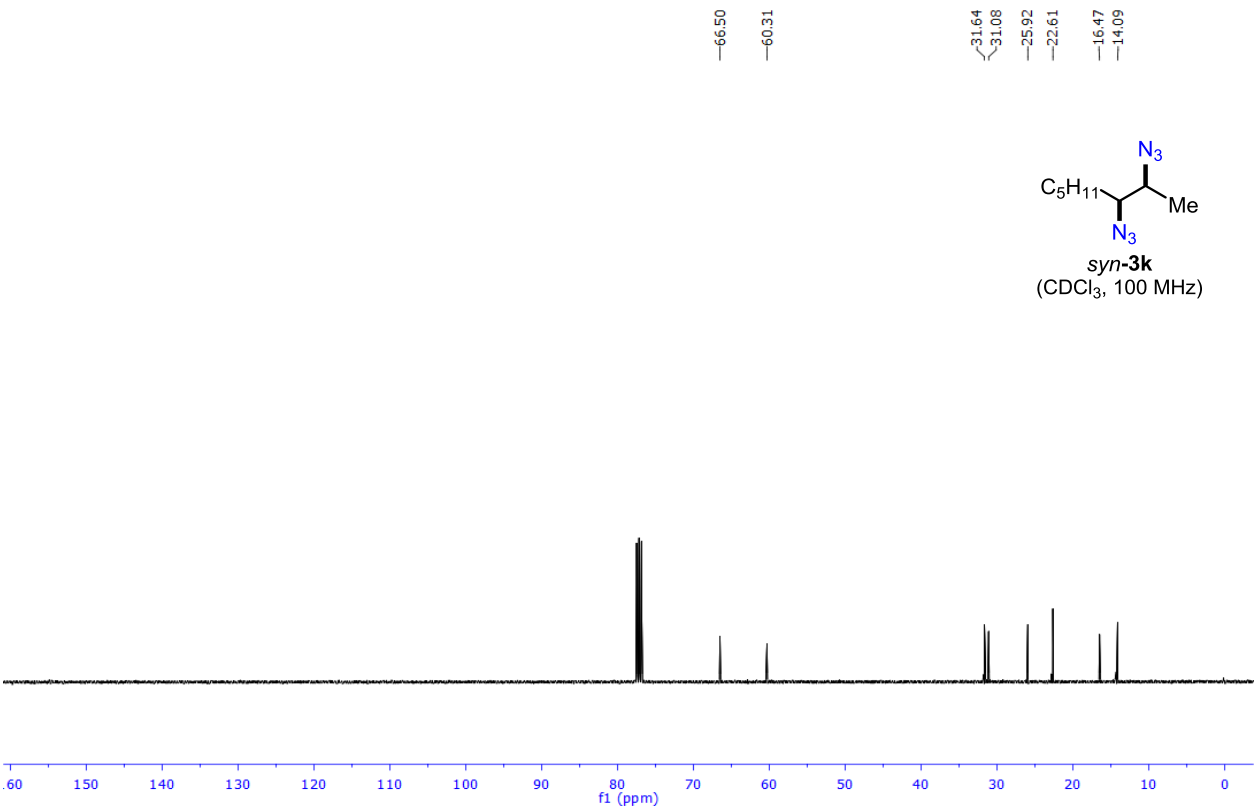
S16
(DMSO-*d6*, 100 MHz)
dr = 2.5:1



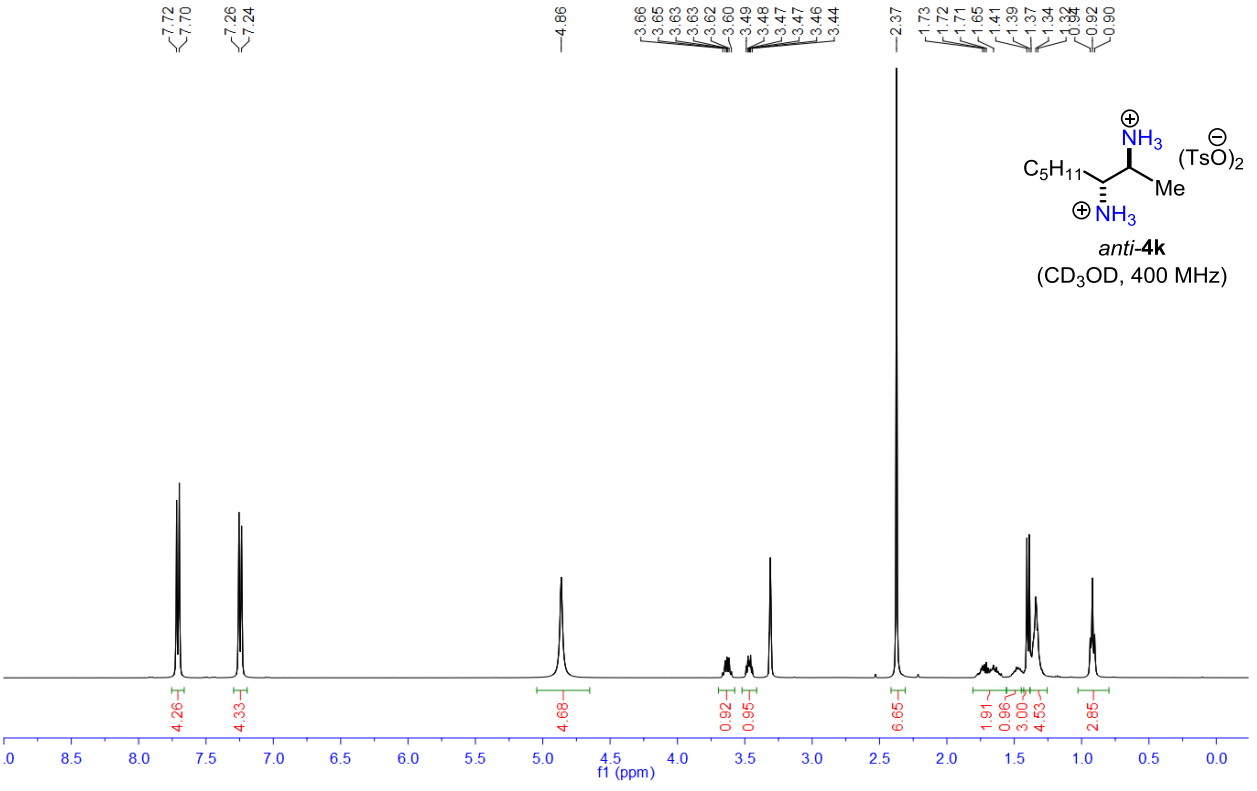
anti-**3k**
($CDCl_3$, 400 MHz)


66.54
60.36
31.60
30.89
26.09
22.59
14.63
14.06
N3
C5H11
Me
N3
anti-3k
(CDCl3, 100 MHz)
f1 (ppm)

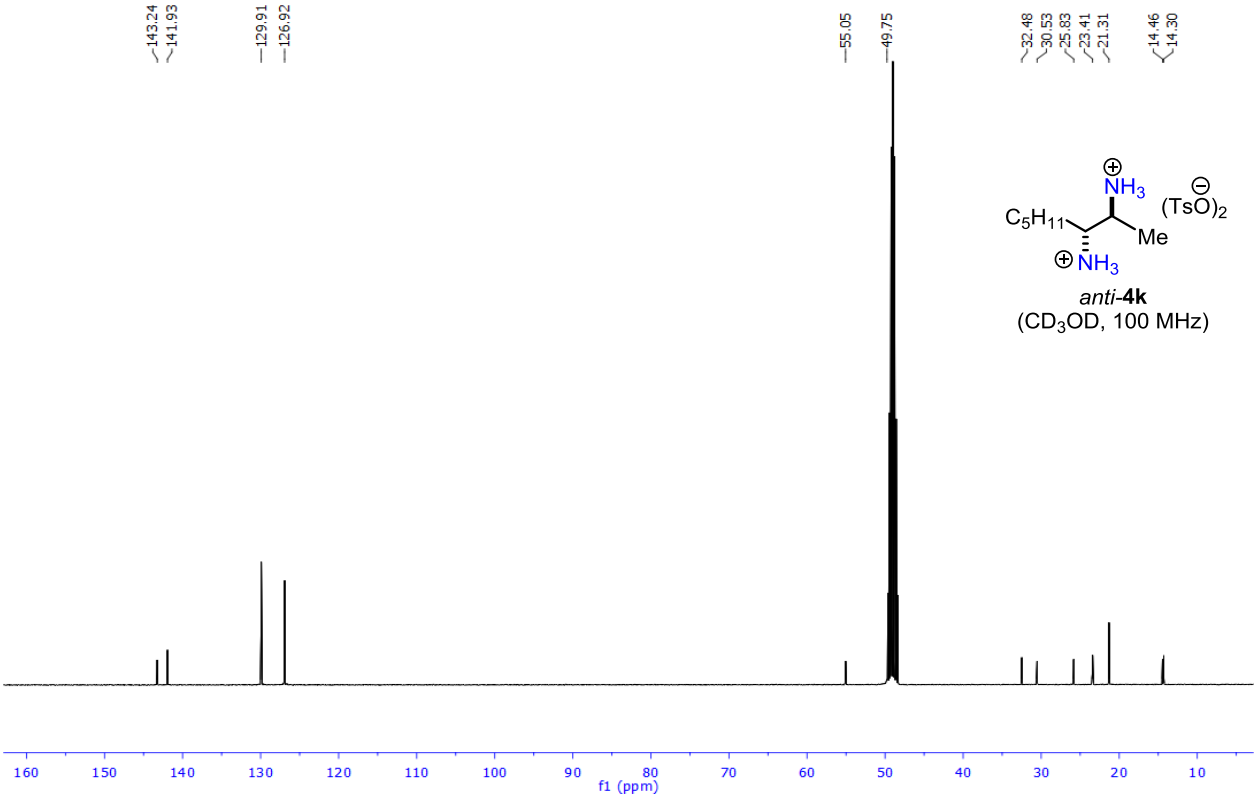

3.55
3.53
3.52
3.52
3.50
3.49
3.19
3.18
3.16
3.15
1.62
1.62
1.60
1.60
1.59
1.57
1.54
1.51
1.49
1.48
1.46
1.44
1.43
1.35
1.33
1.32
1.31
0.92
0.91
0.89
N3
C5H11
Me
N3
syn-3k
(CDCl3, 400 MHz)
1.06
1.00
2.03
2.16
7.03
3.02
f1 (ppm)



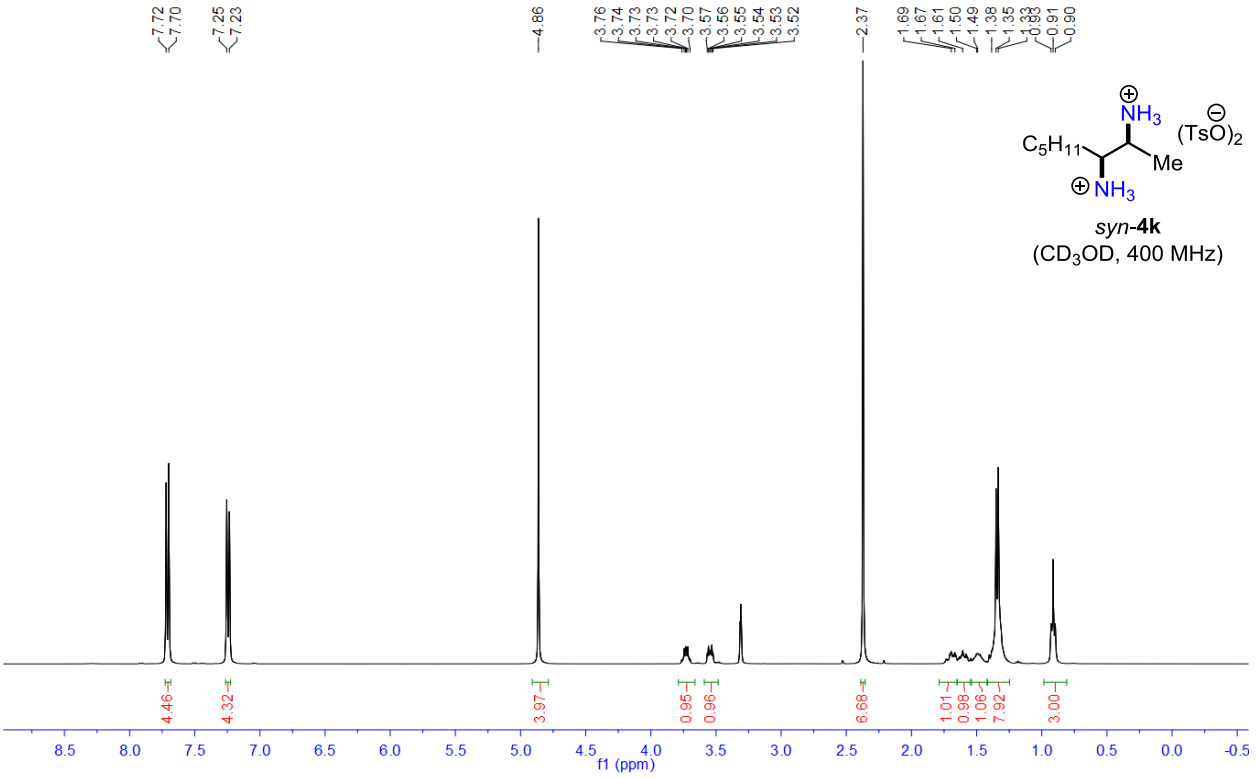
syn-**3k**
($CDCl_3$, 100 MHz)



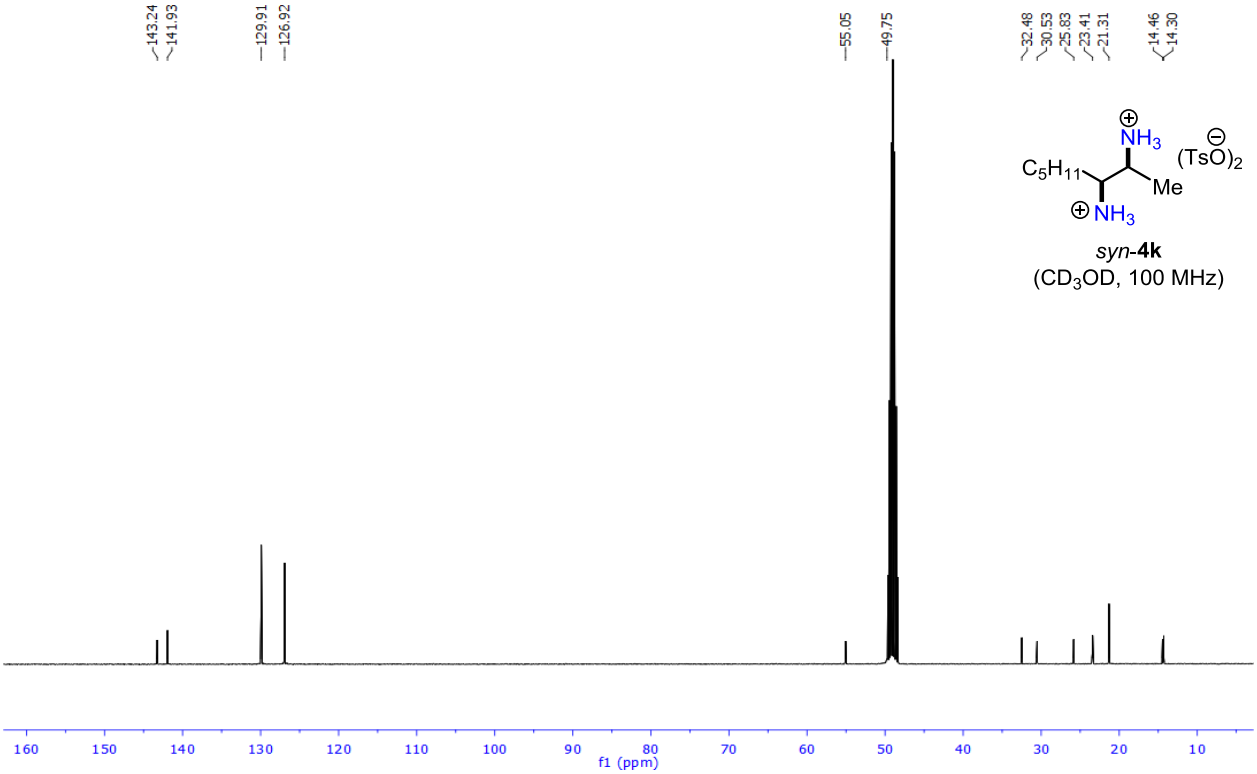
anti-**4k**
(CD_3OD, 400 MHz)



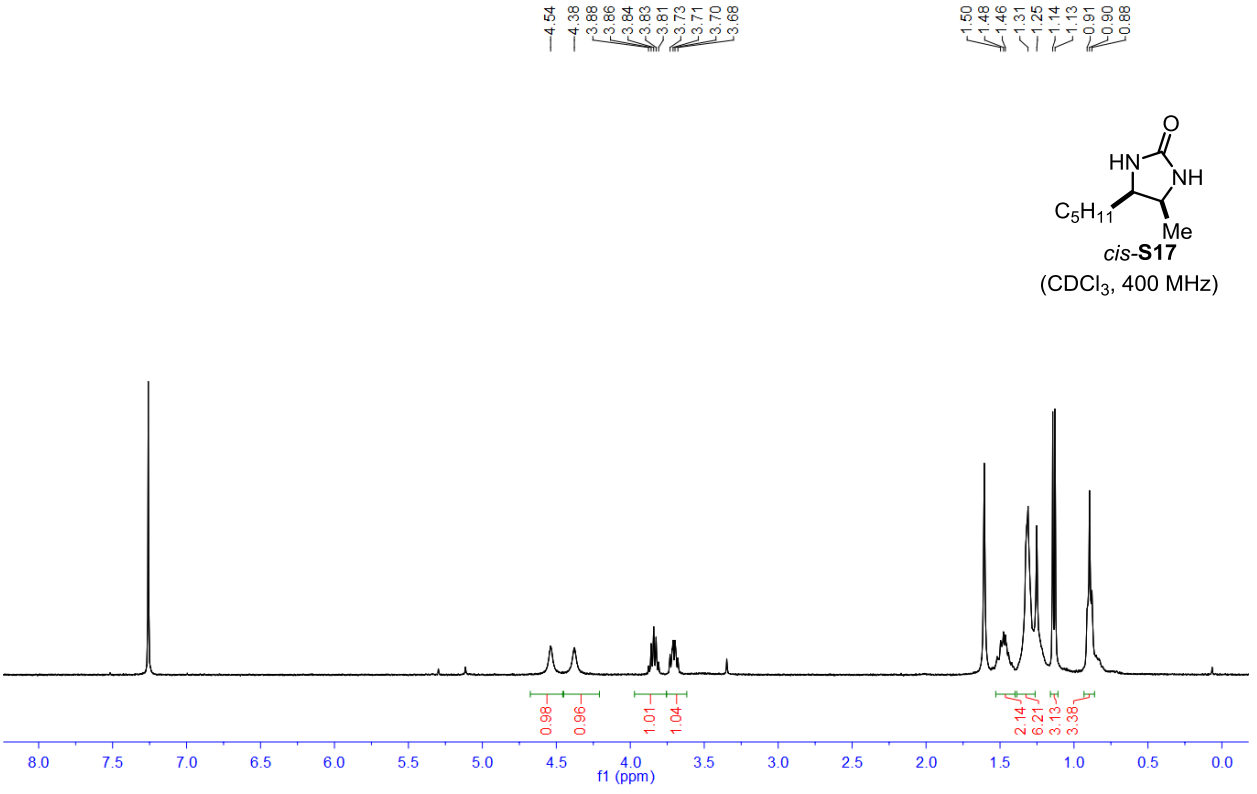
anti-**4k**
(CD_3OD, 100 MHz)



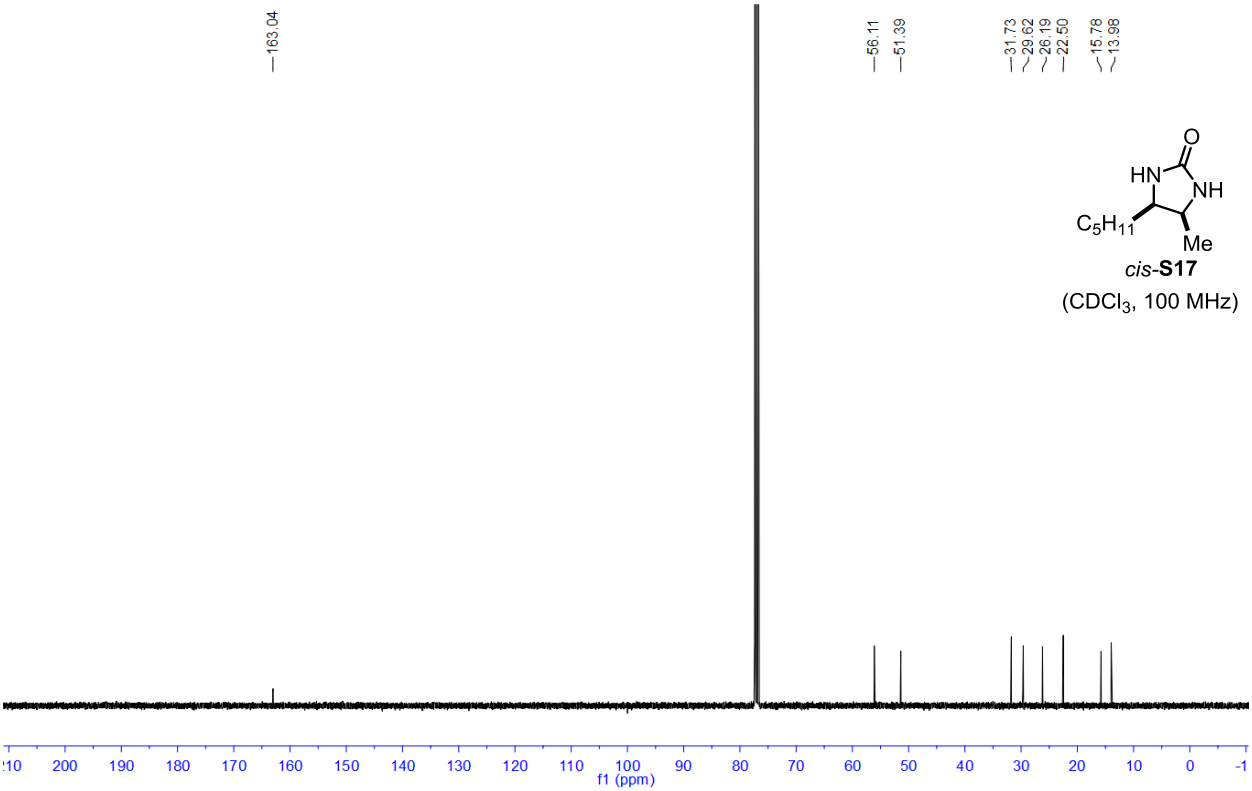
syn-**4k**
(CD_3OD, 400 MHz)



syn-**4k**
(CD_3OD, 100 MHz)

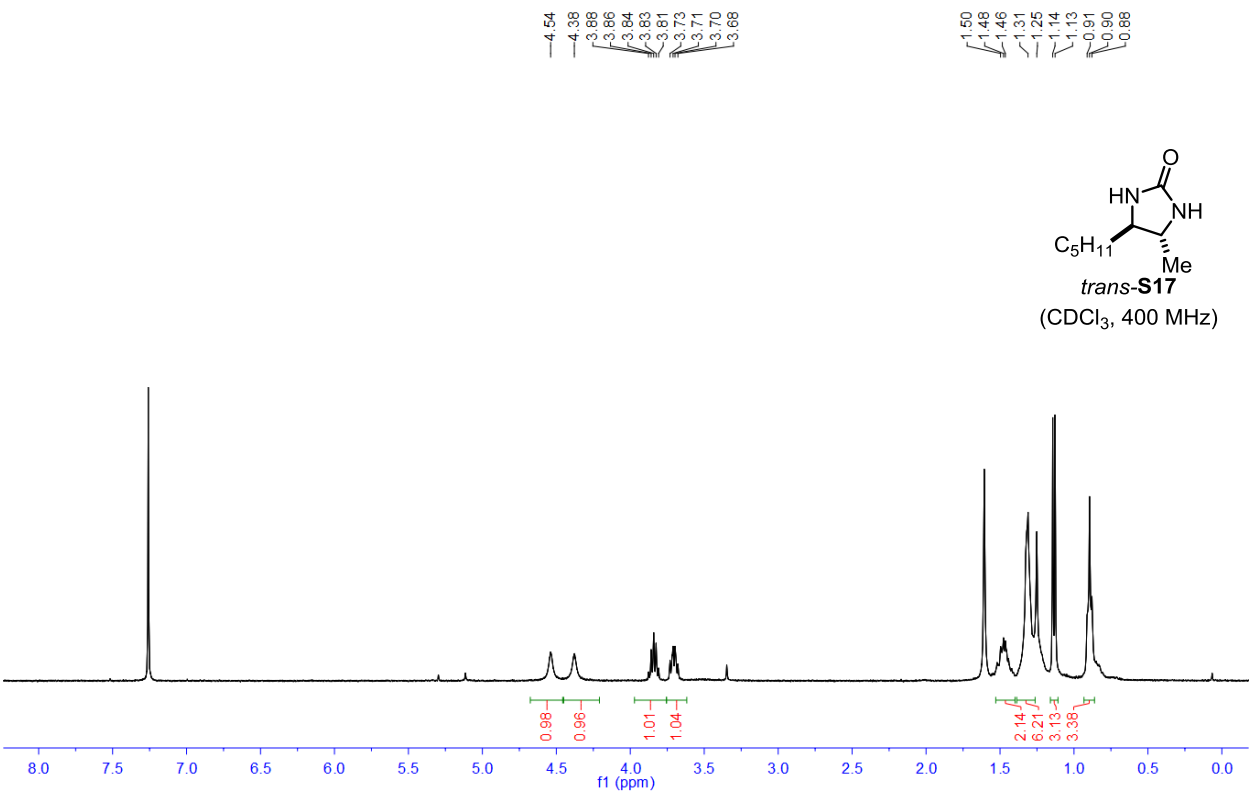


cis-**S17**
($CDCl_3$, 400 MHz)



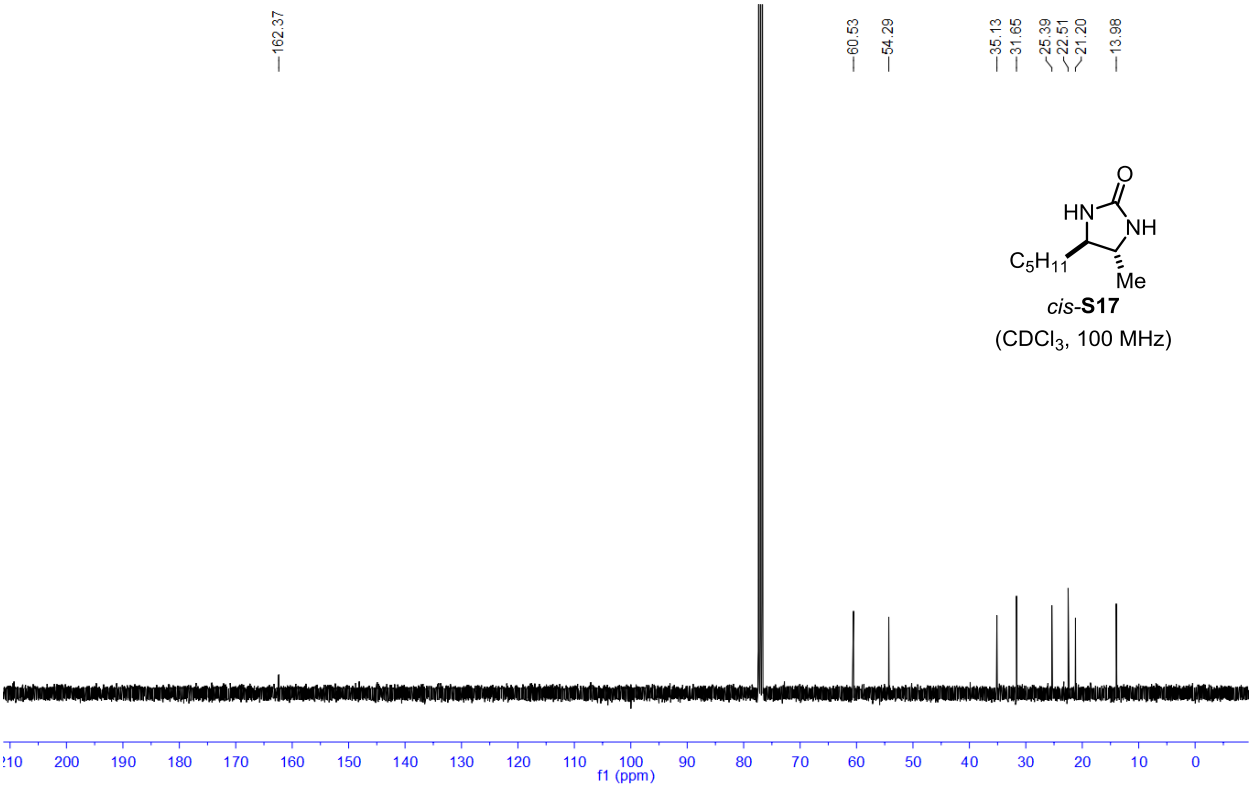
cis-**S17**

($CDCl_3$, 100 MHz)



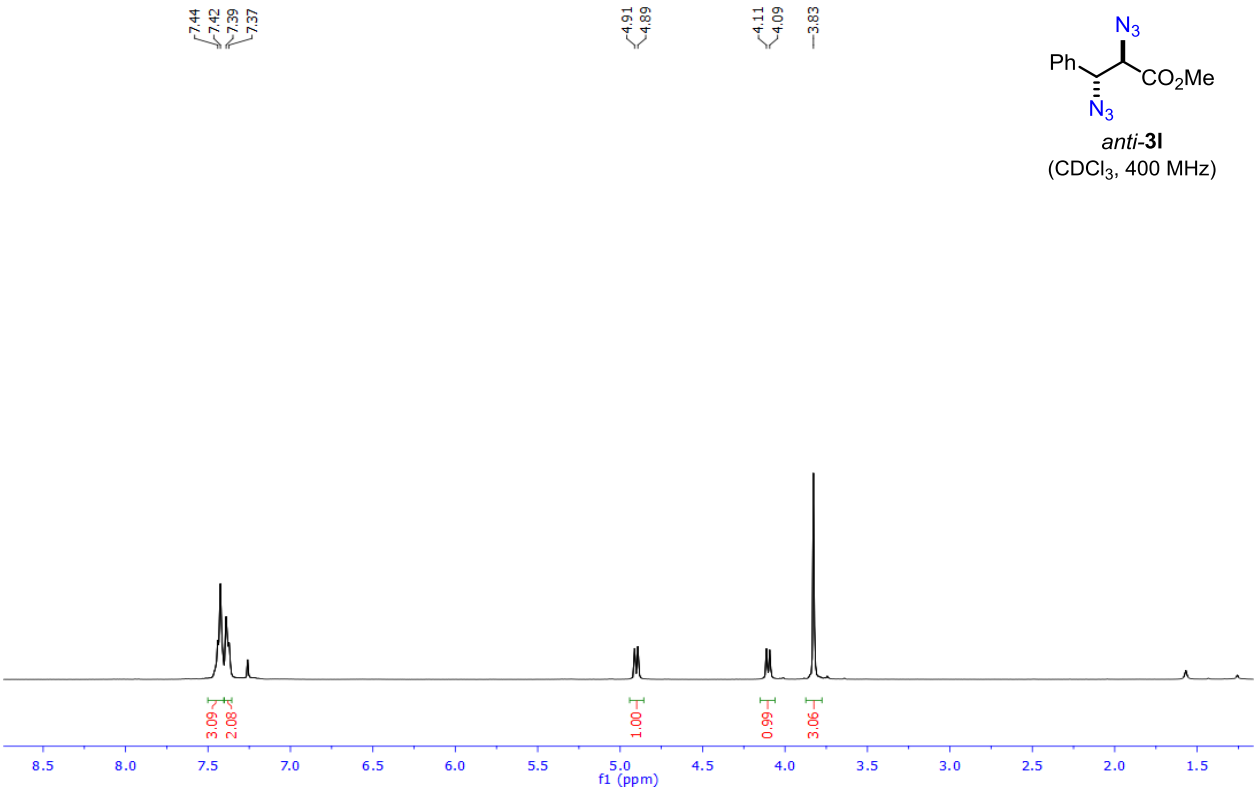
trans-**S17**

($CDCl_3$, 400 MHz)



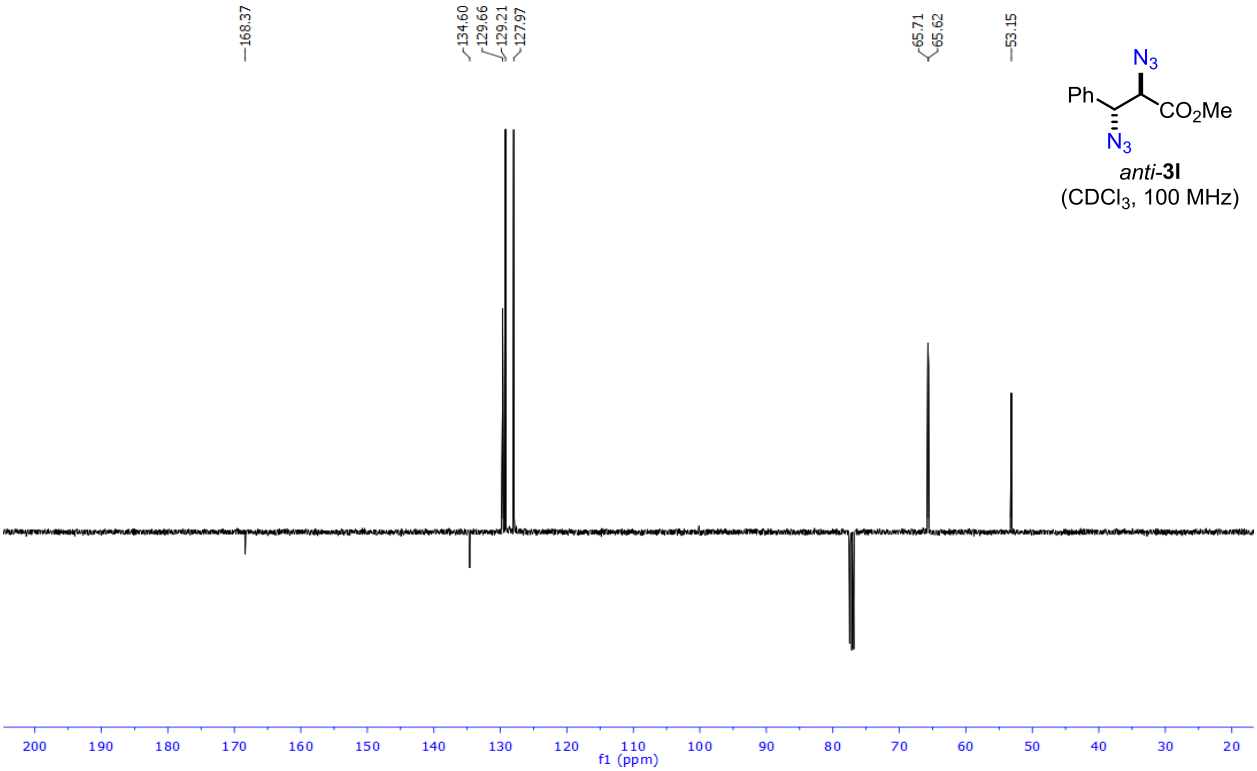
cis-**S17**

($CDCl_3$, 100 MHz)

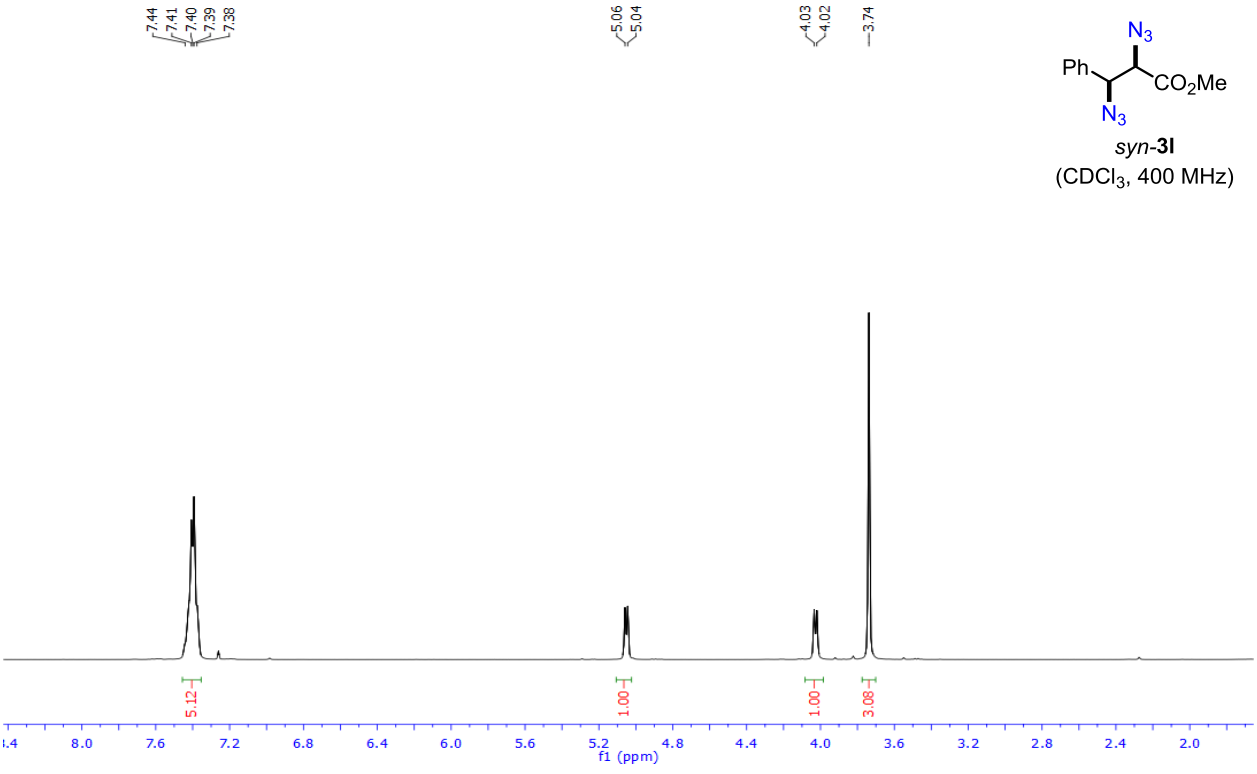


anti-**3l**

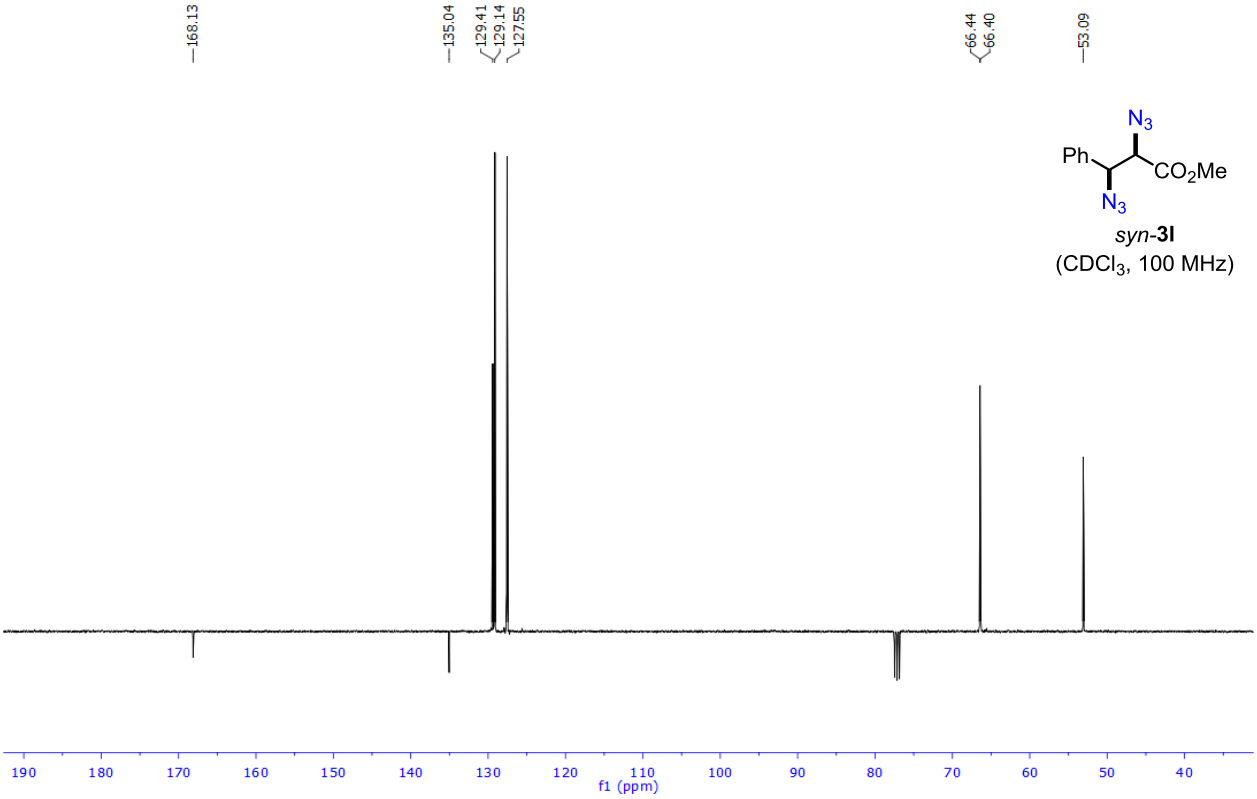
($CDCl_3$, 400 MHz)



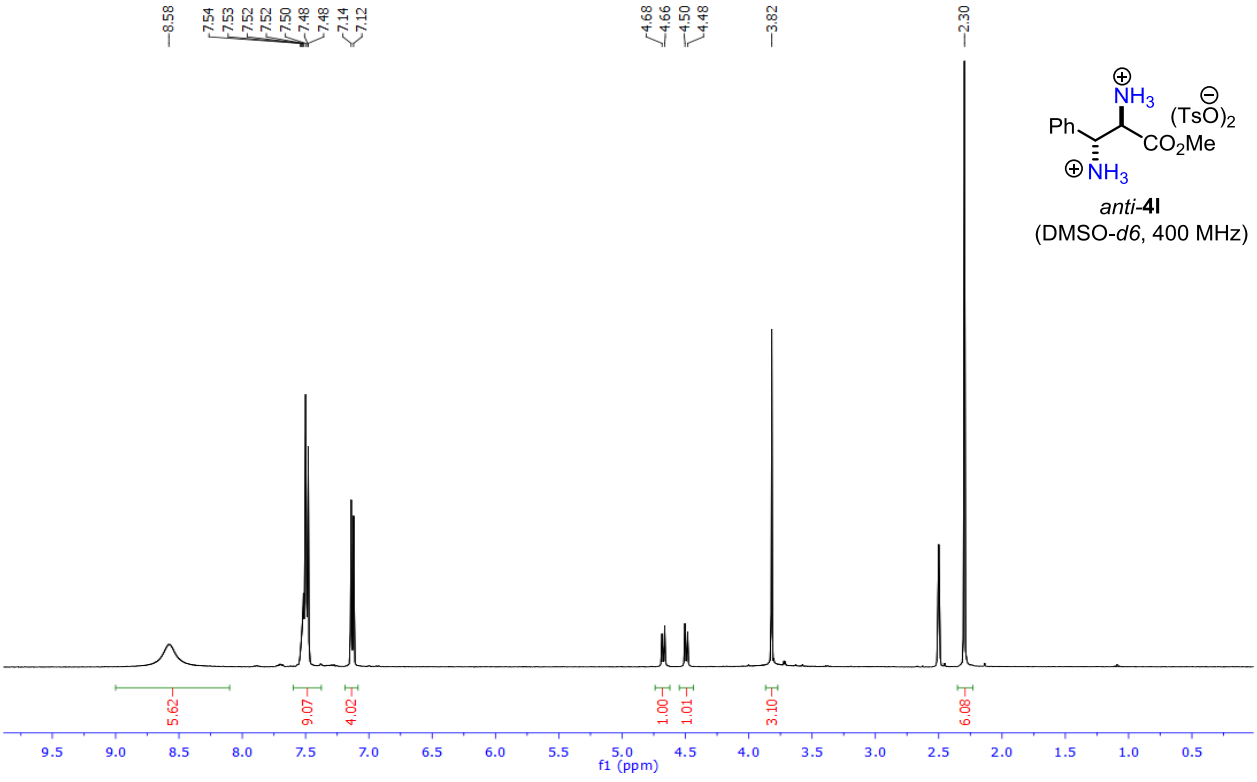
anti-**3l**
($CDCl_3$, 100 MHz)



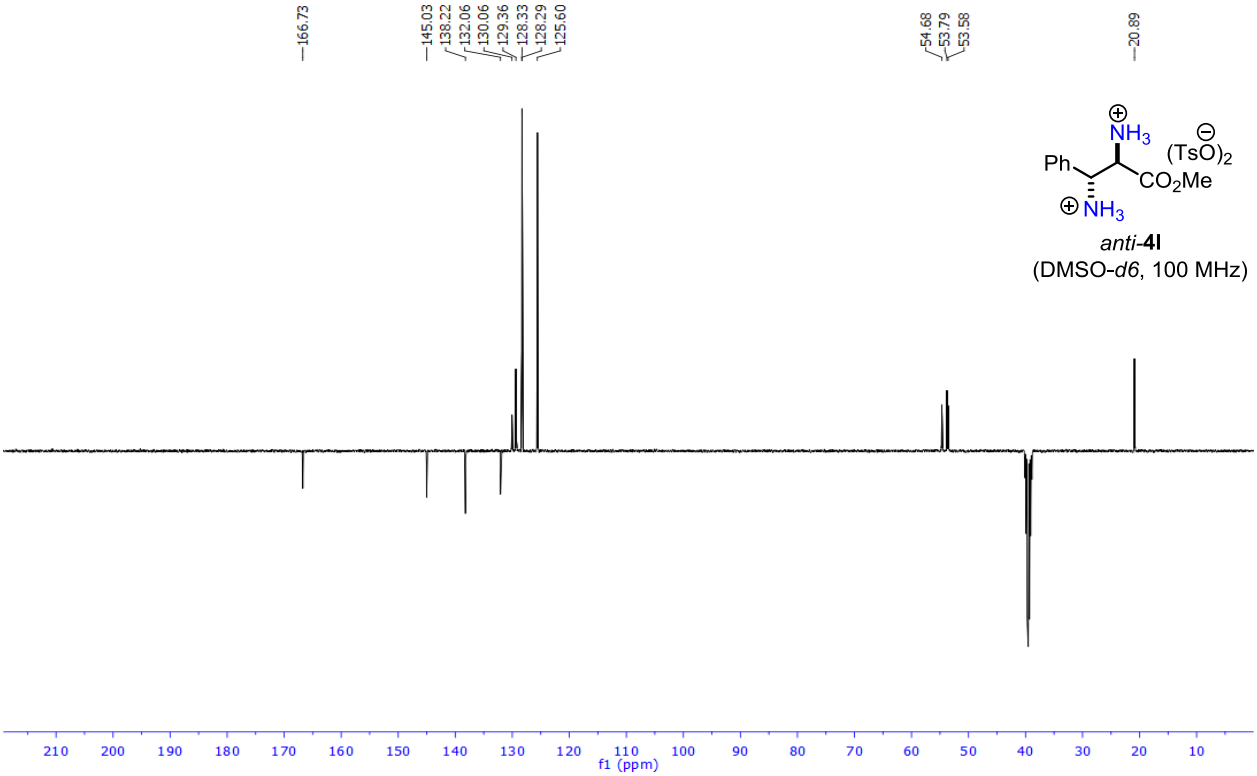
syn-**3l**
($CDCl_3$, 400 MHz)



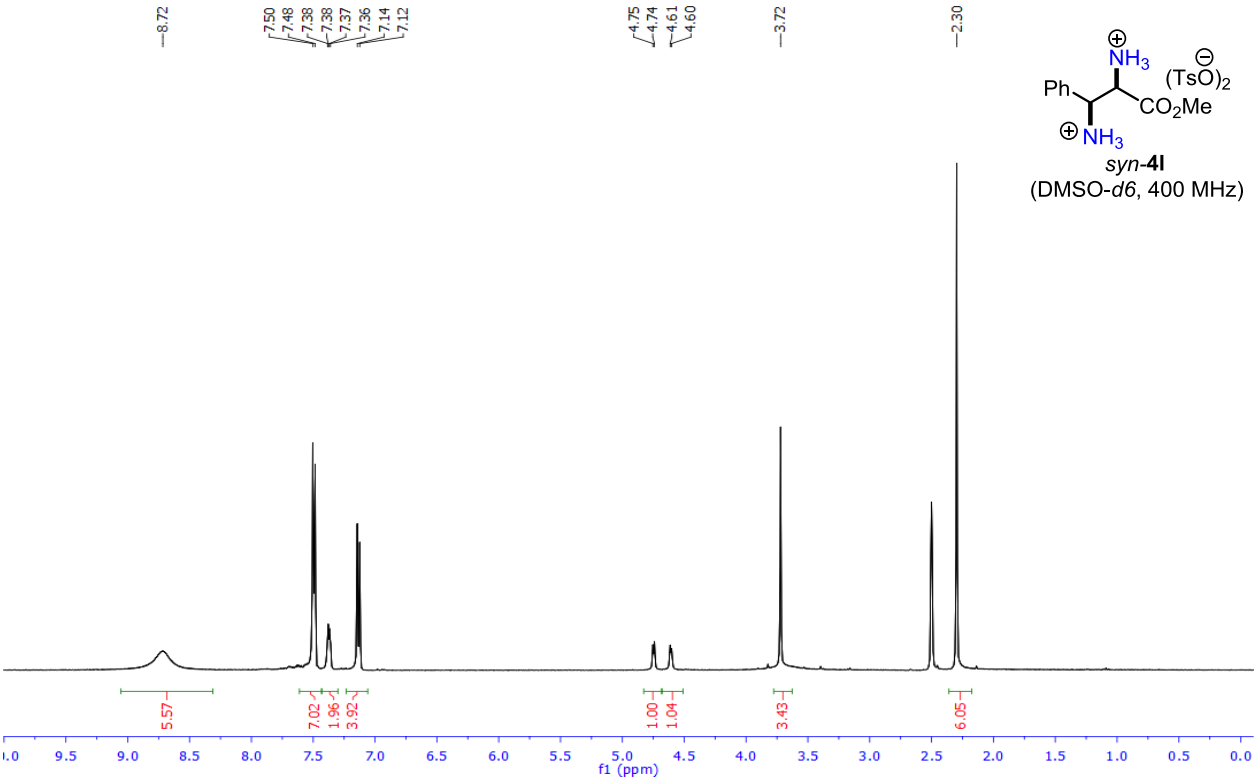
syn-**3l**
($CDCl_3$, 100 MHz)



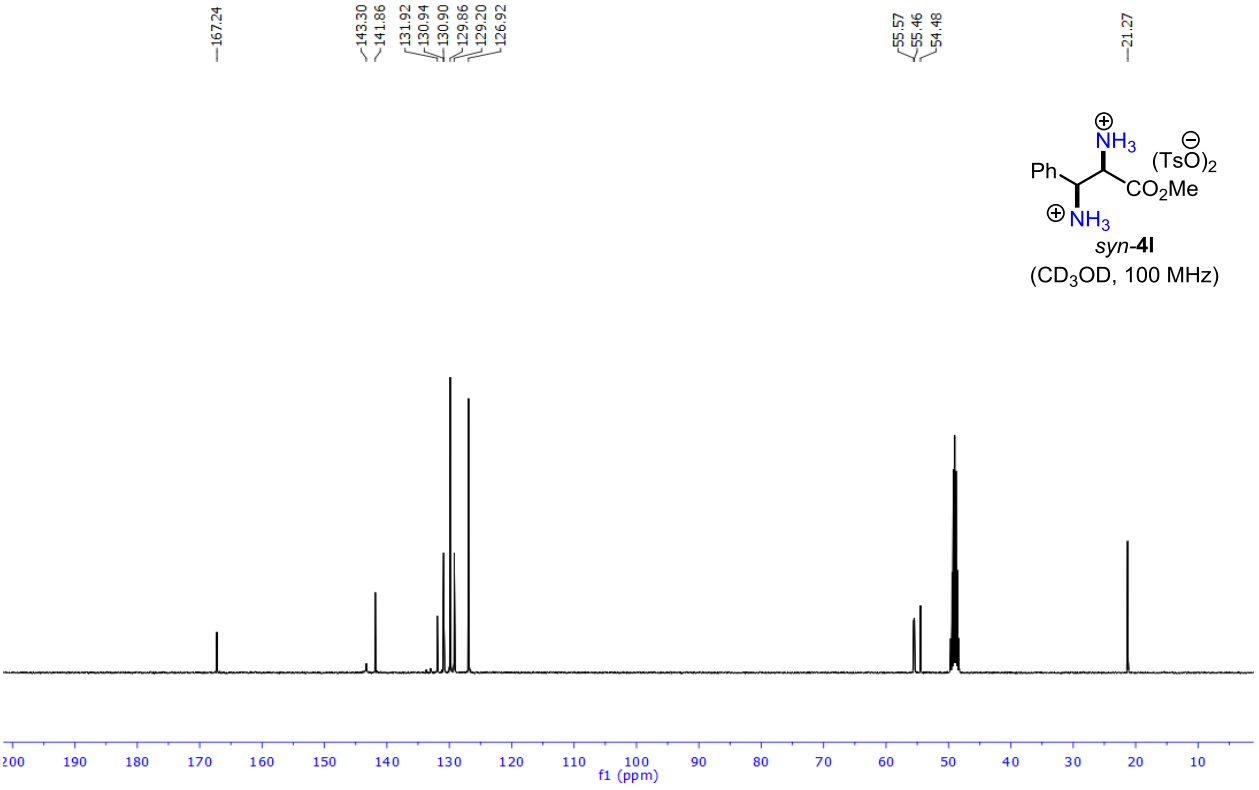
anti-**4l**
(DMSO-*d6*, 400 MHz)



anti-**4l**
(DMSO-*d6*, 100 MHz)

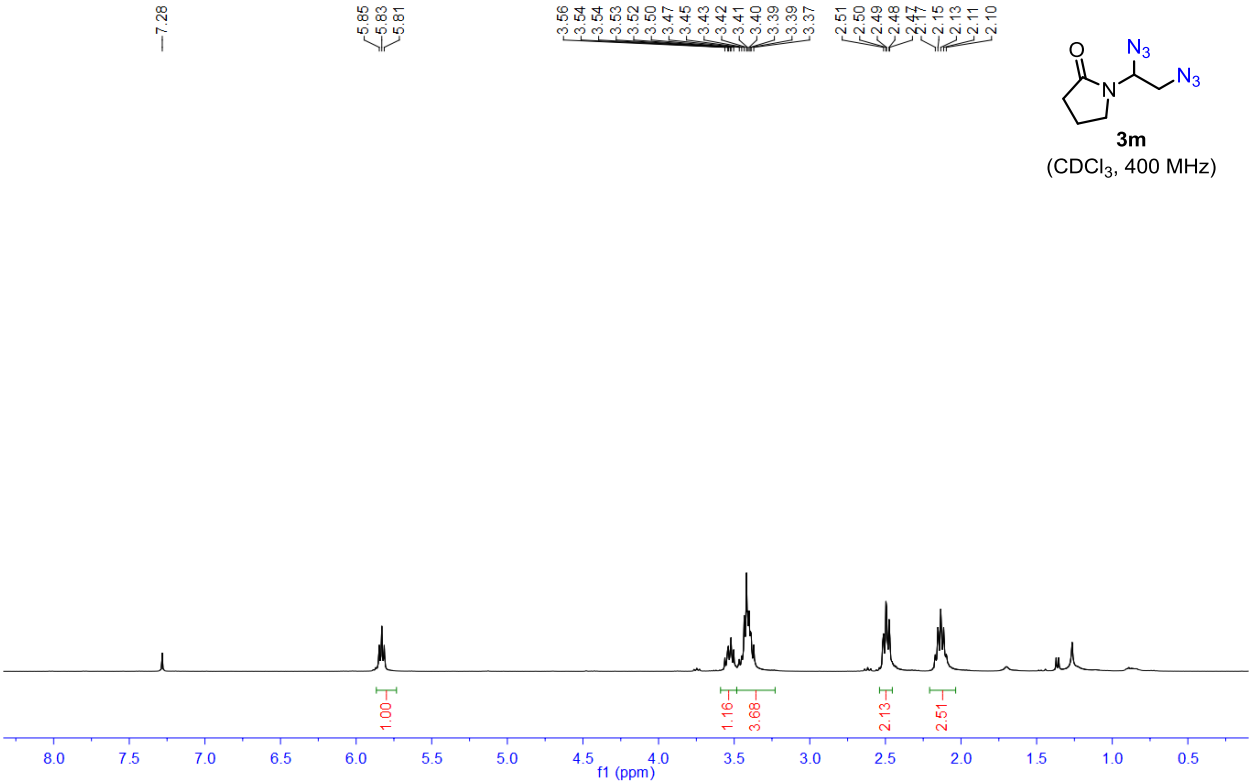


syn-**4l**
(DMSO-*d6*, 400 MHz)



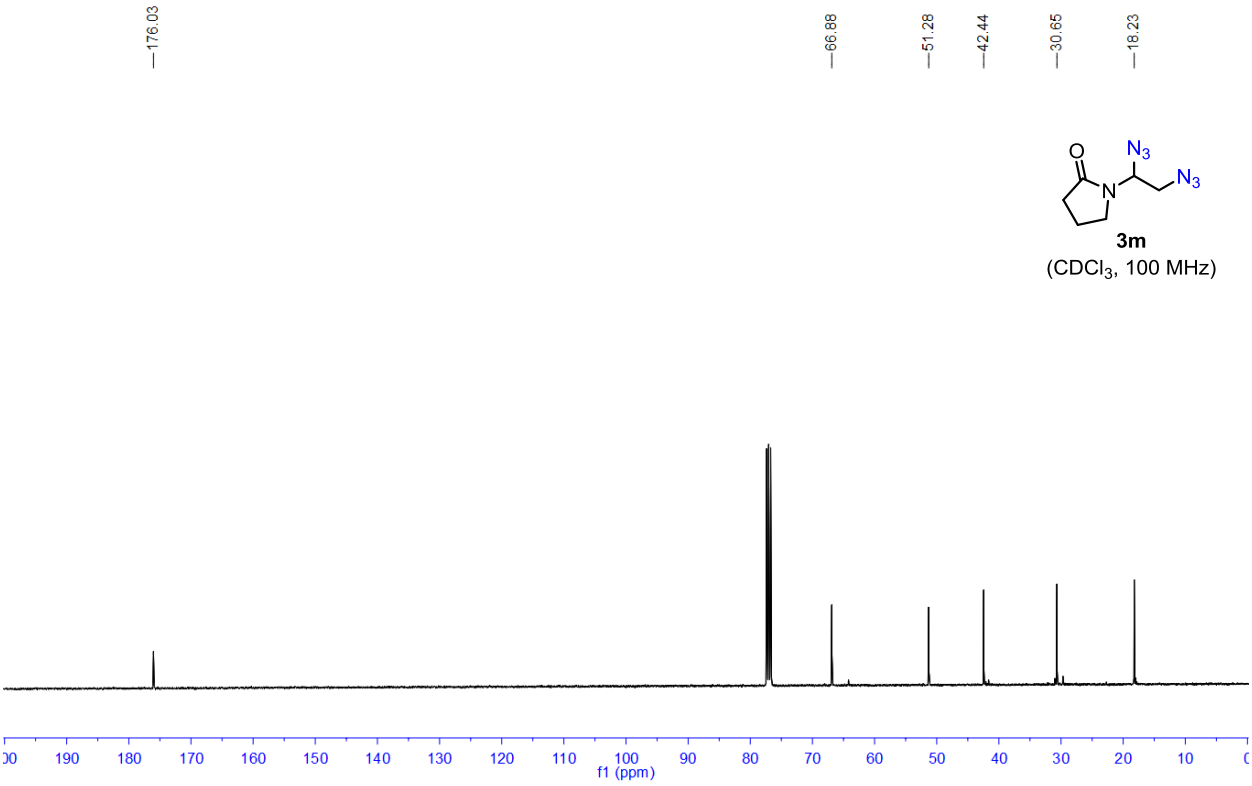
syn-**4l**

(CD_3OD, 100 MHz)

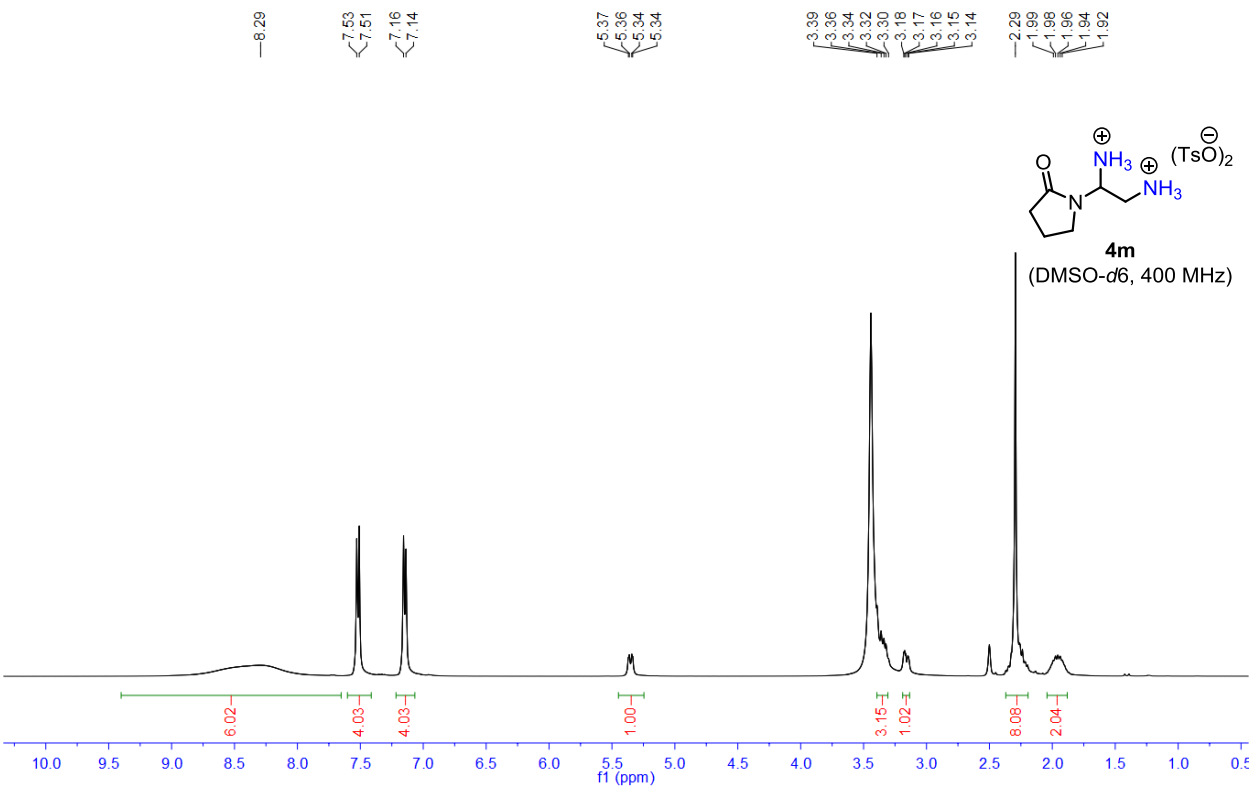


3m

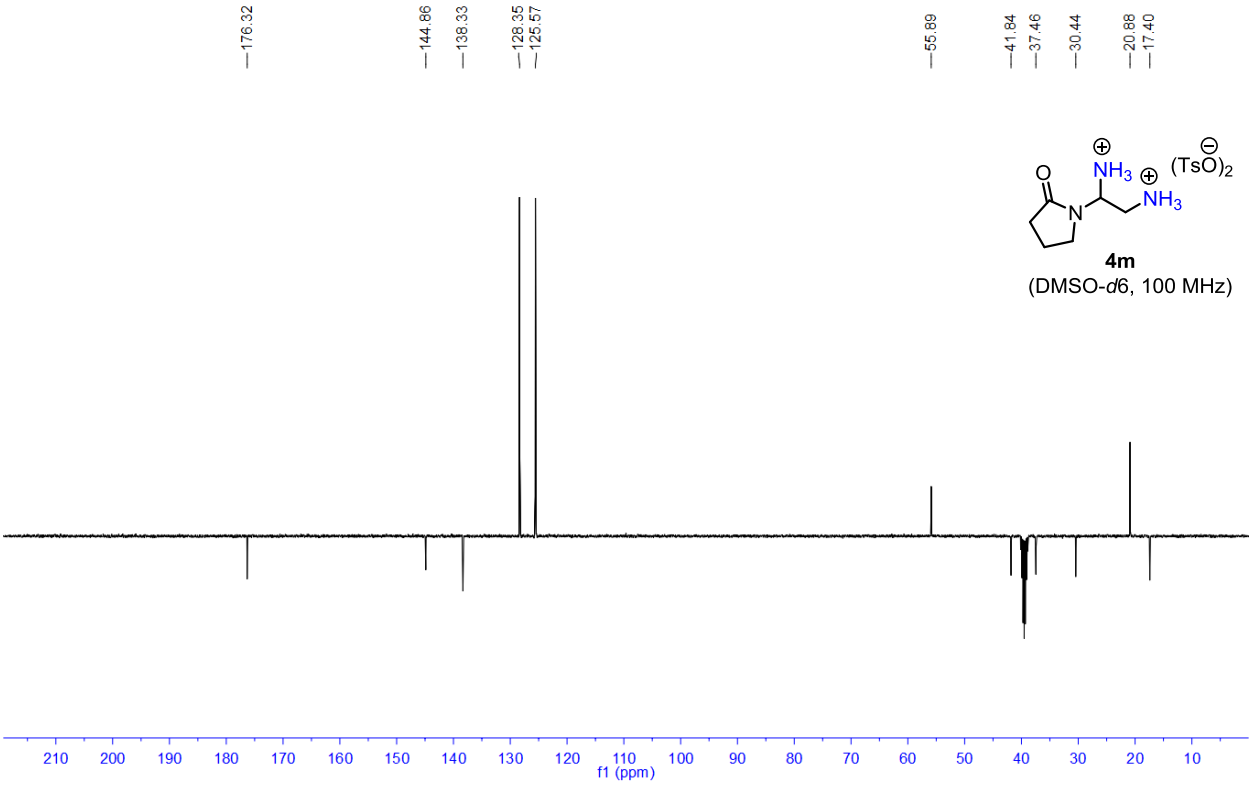
($CDCl_3$, 400 MHz)



3m
($CDCl_3$, 100 MHz)

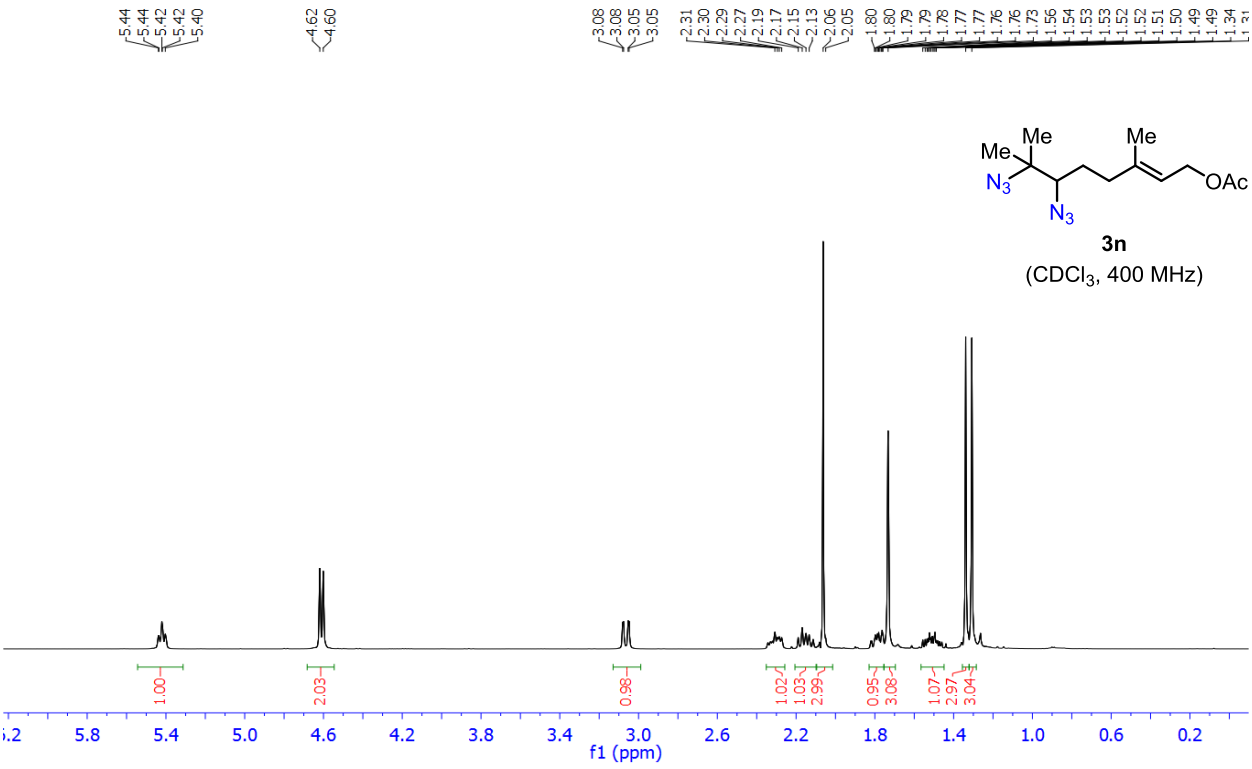


4m
(DMSO-*d*6, 400 MHz)



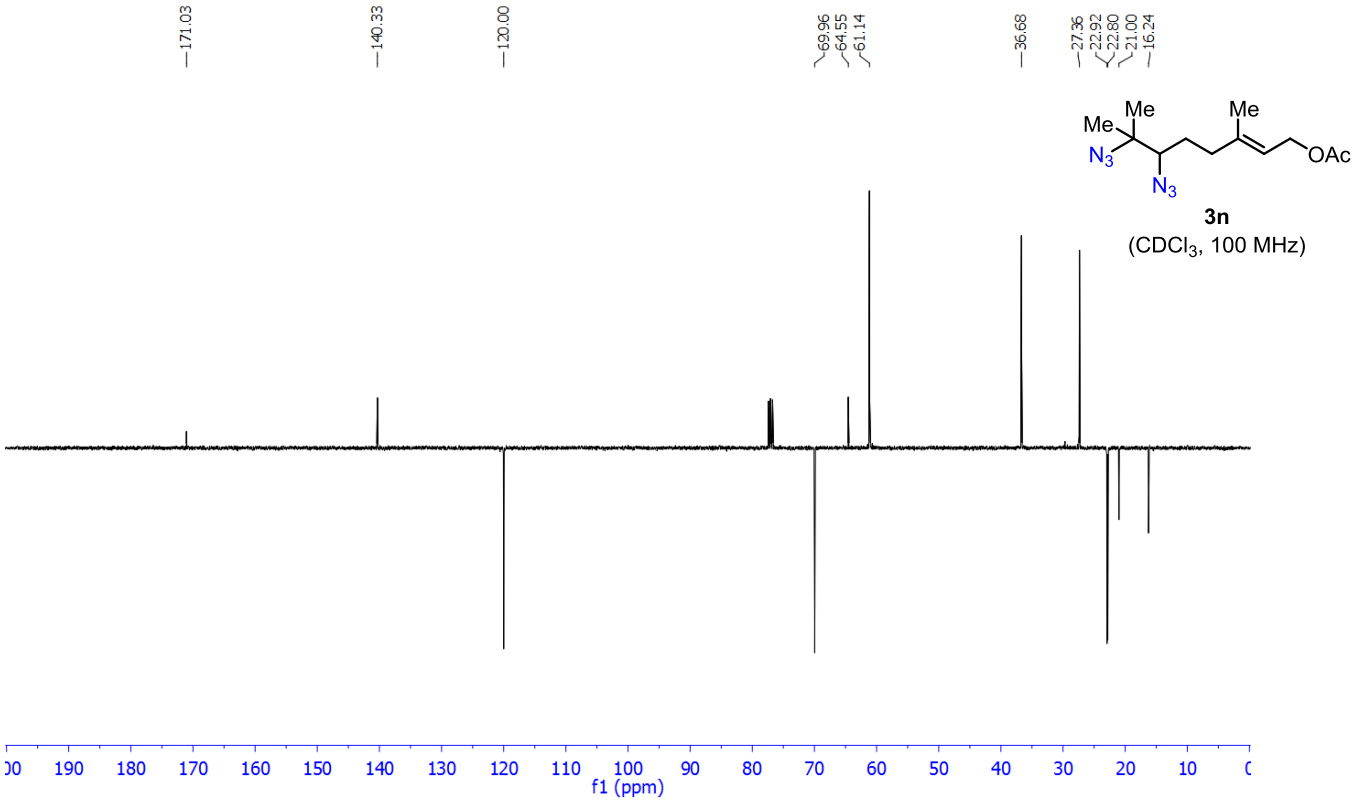
4m

(DMSO-*d*6, 100 MHz)



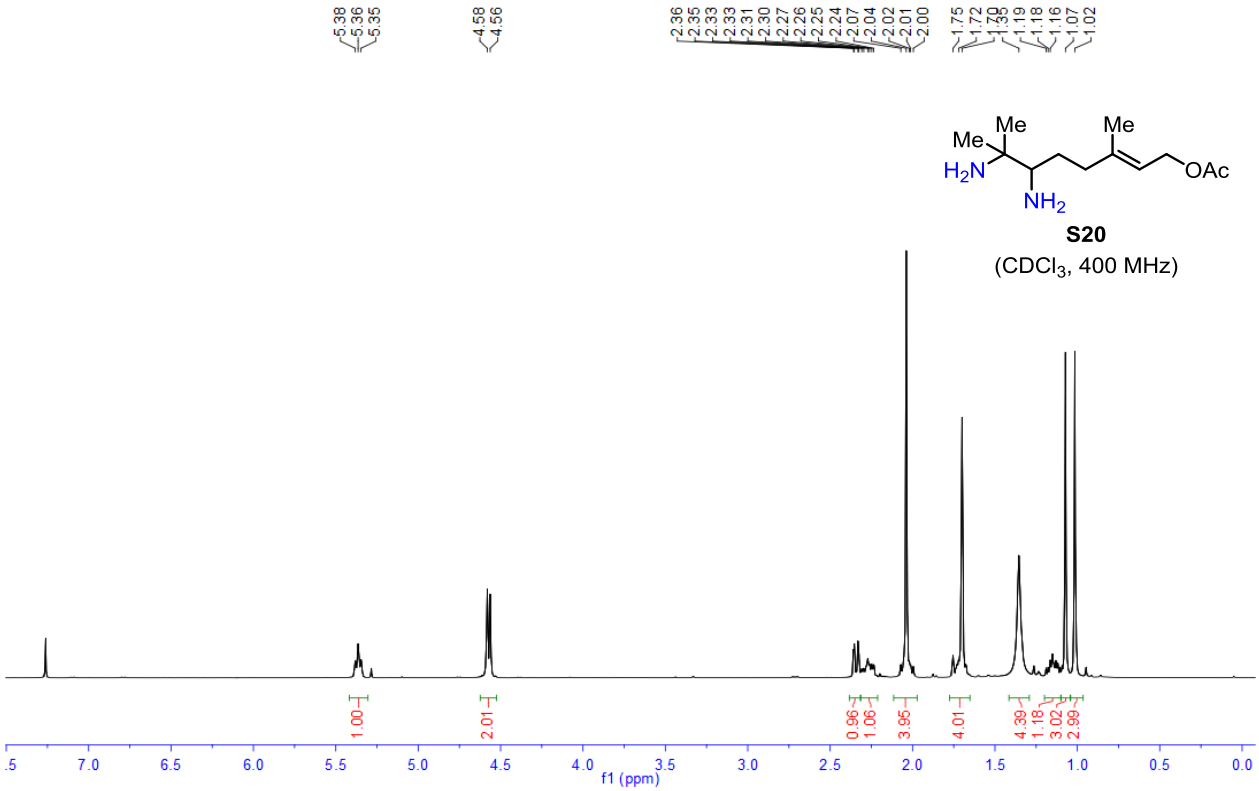
3n

($CDCl_3$, 400 MHz)



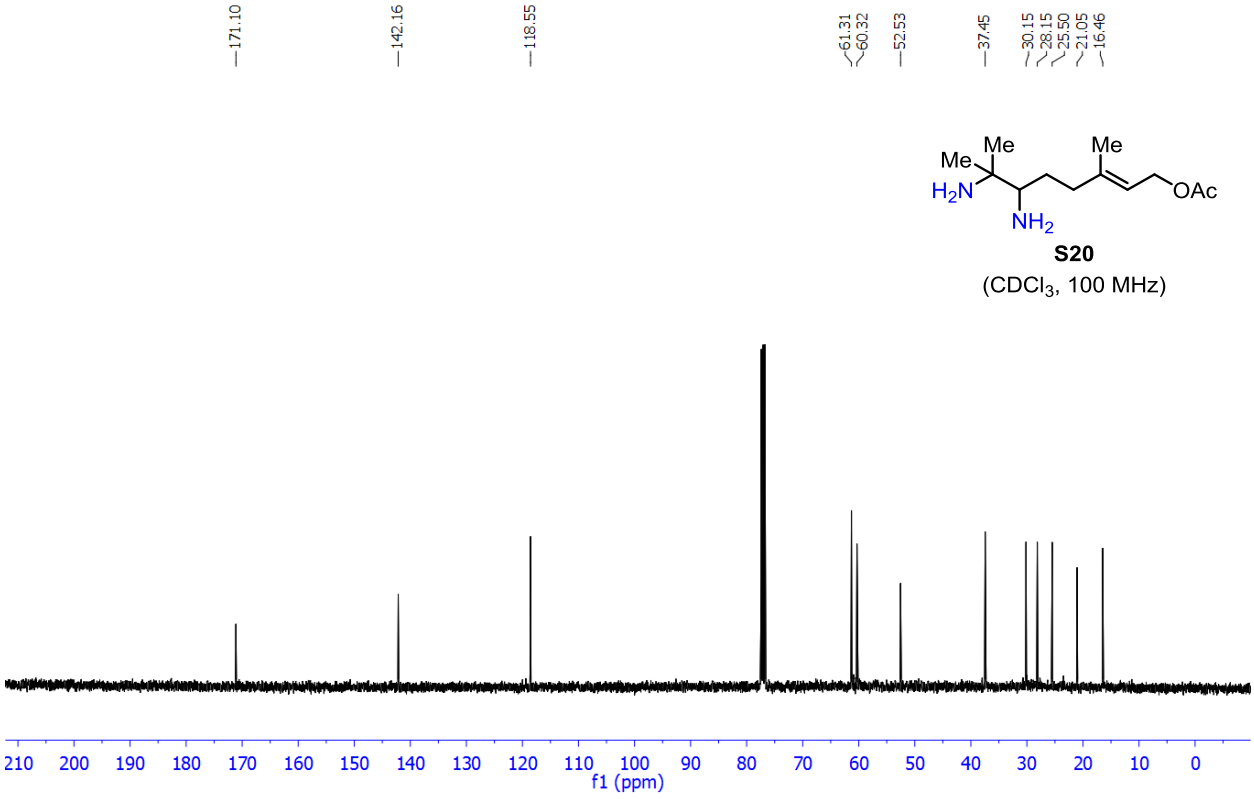
3n

($CDCl_3$, 100 MHz)



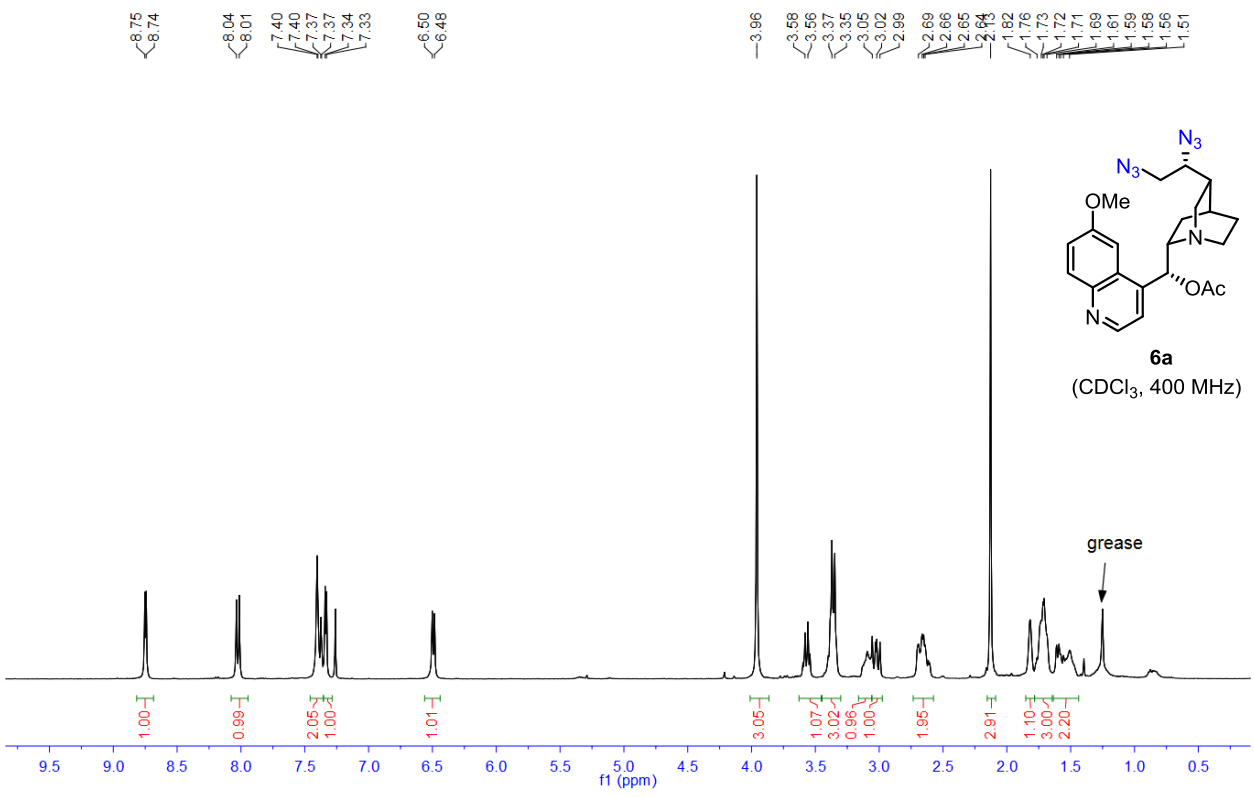
S20

($CDCl_3$, 400 MHz)



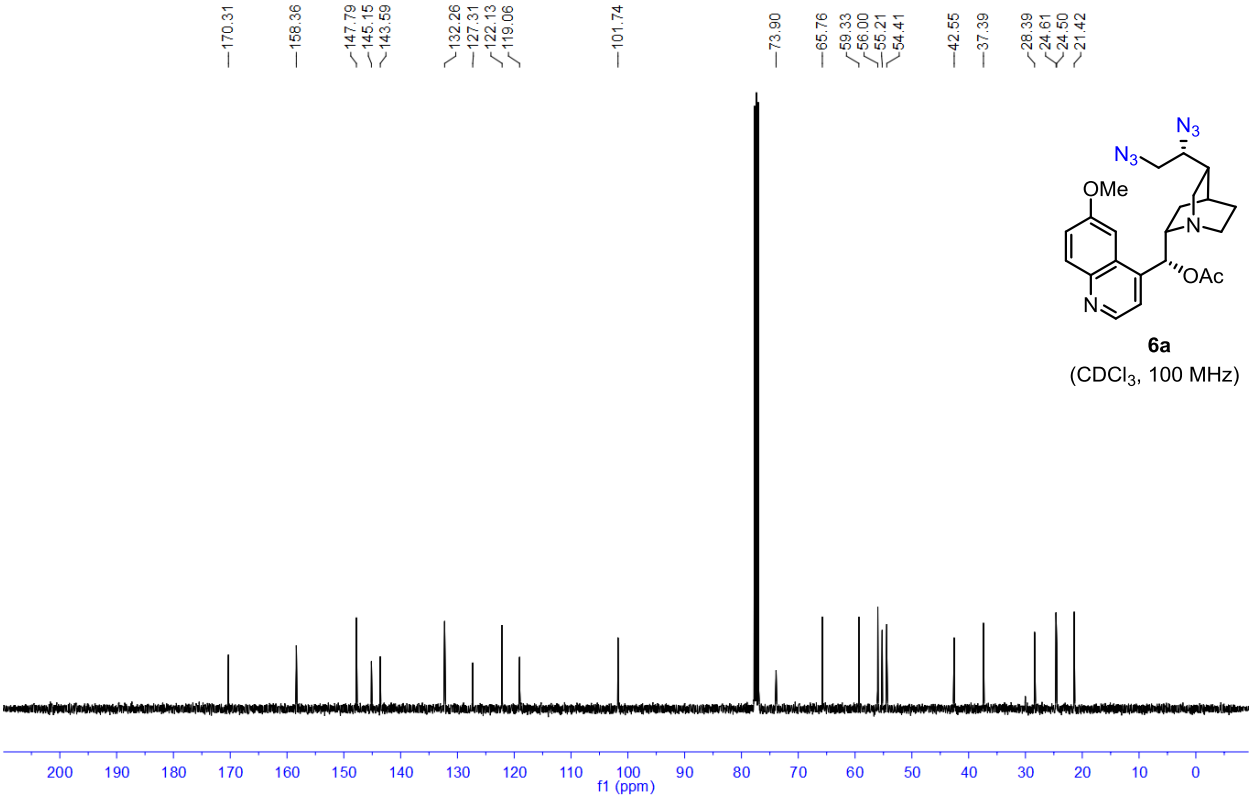
S20

($CDCl_3$, 100 MHz)

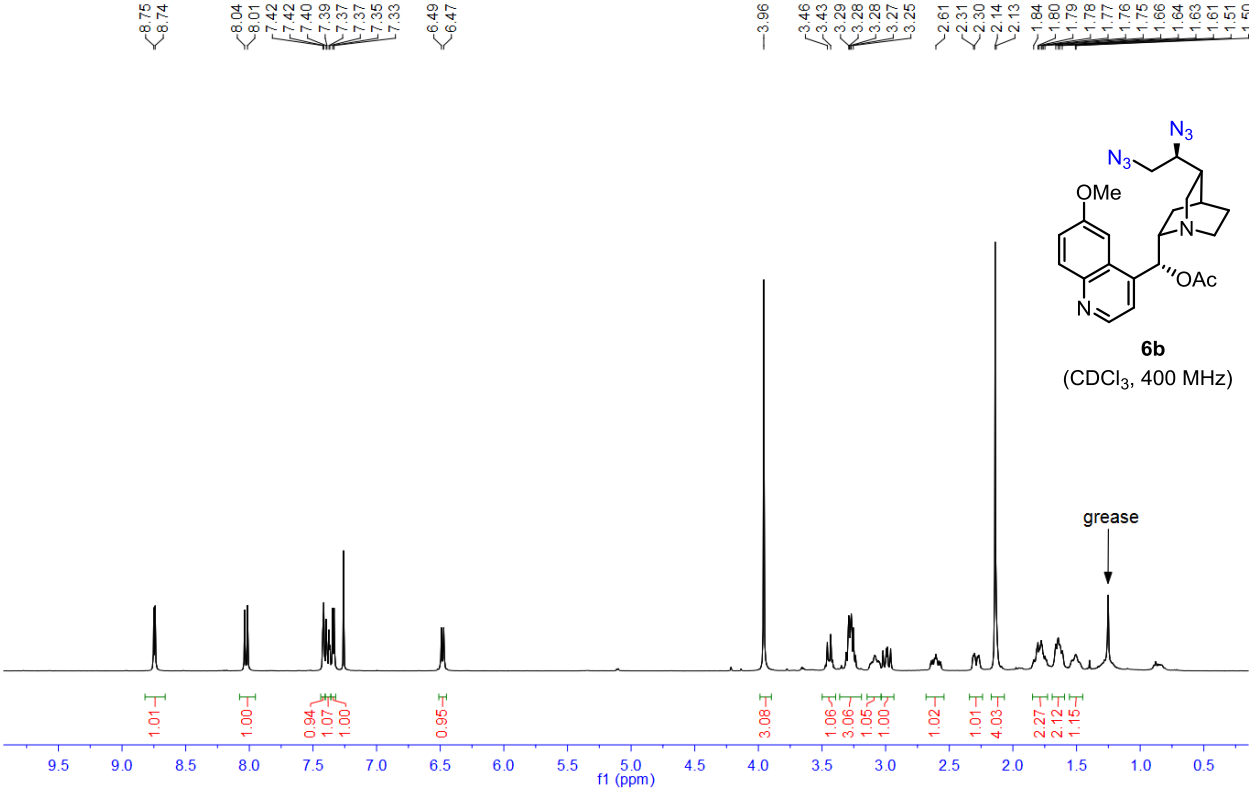


6a

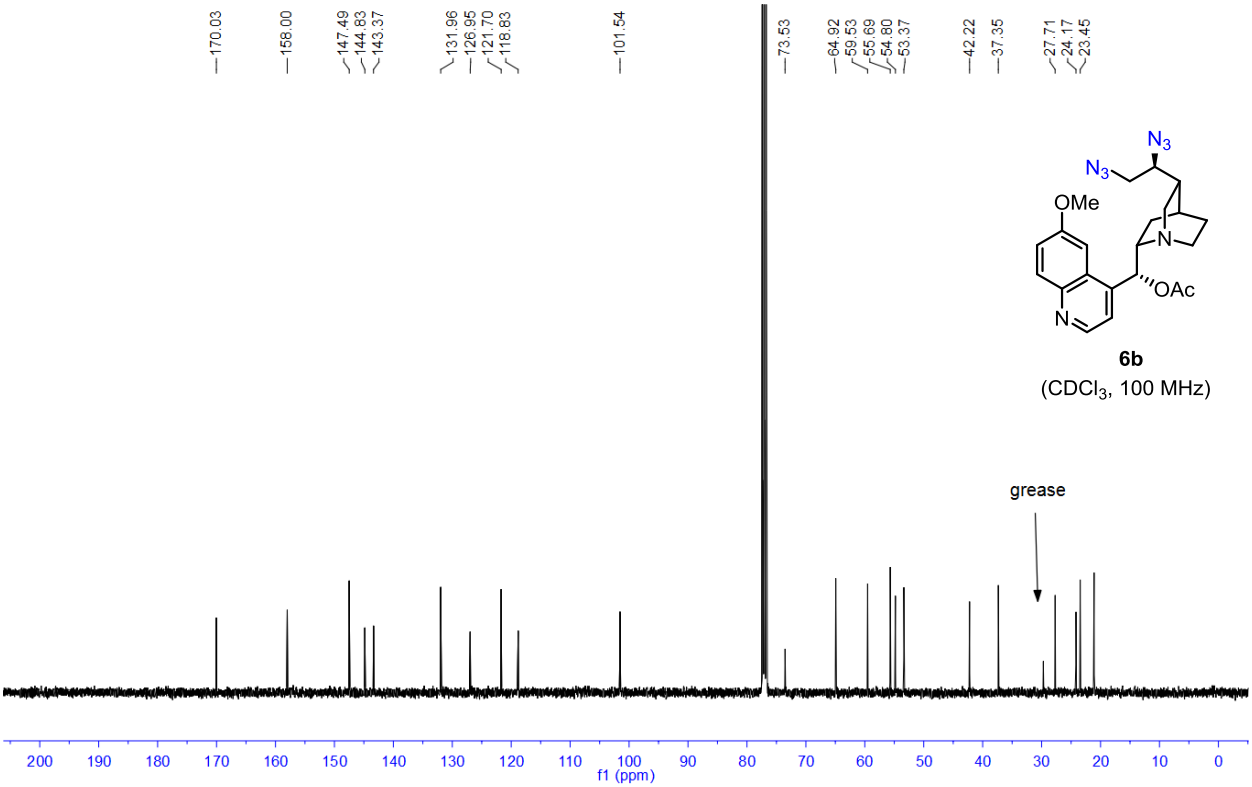
($CDCl_3$, 400 MHz)



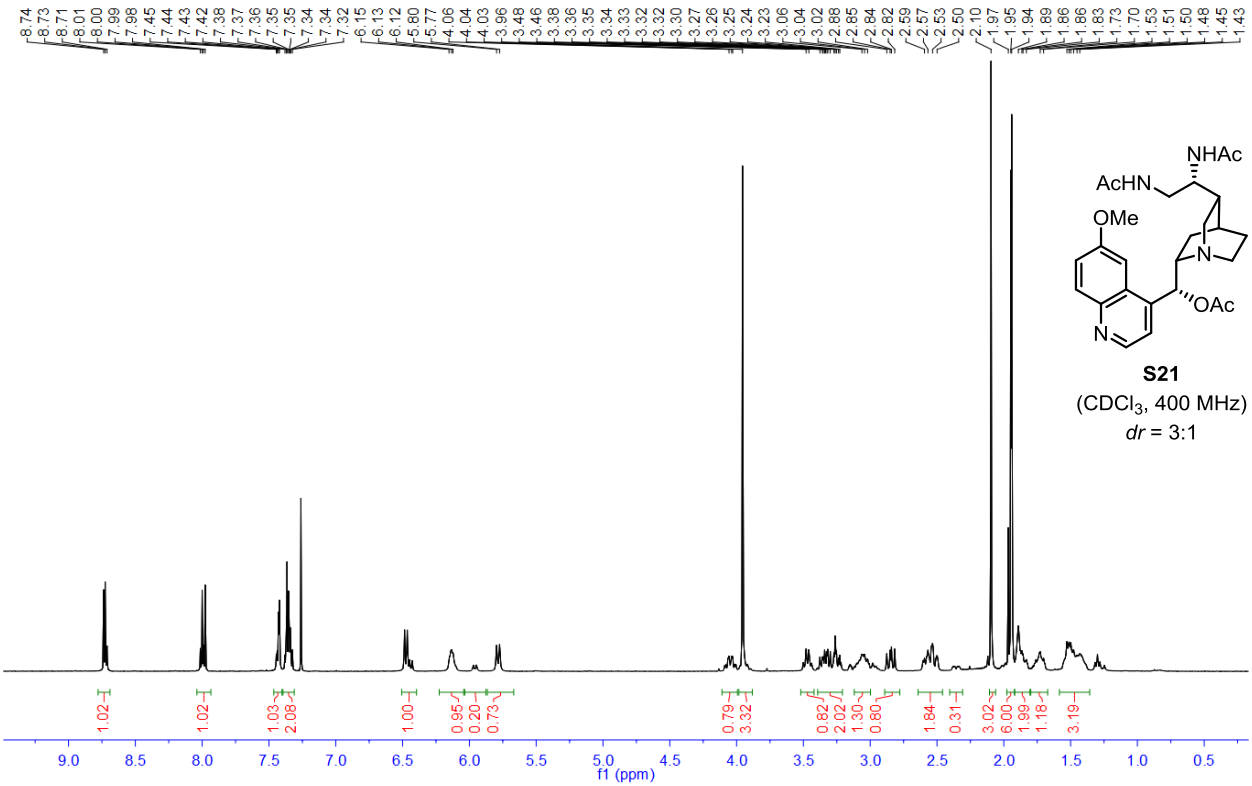
6a
($CDCl_3$, 100 MHz)



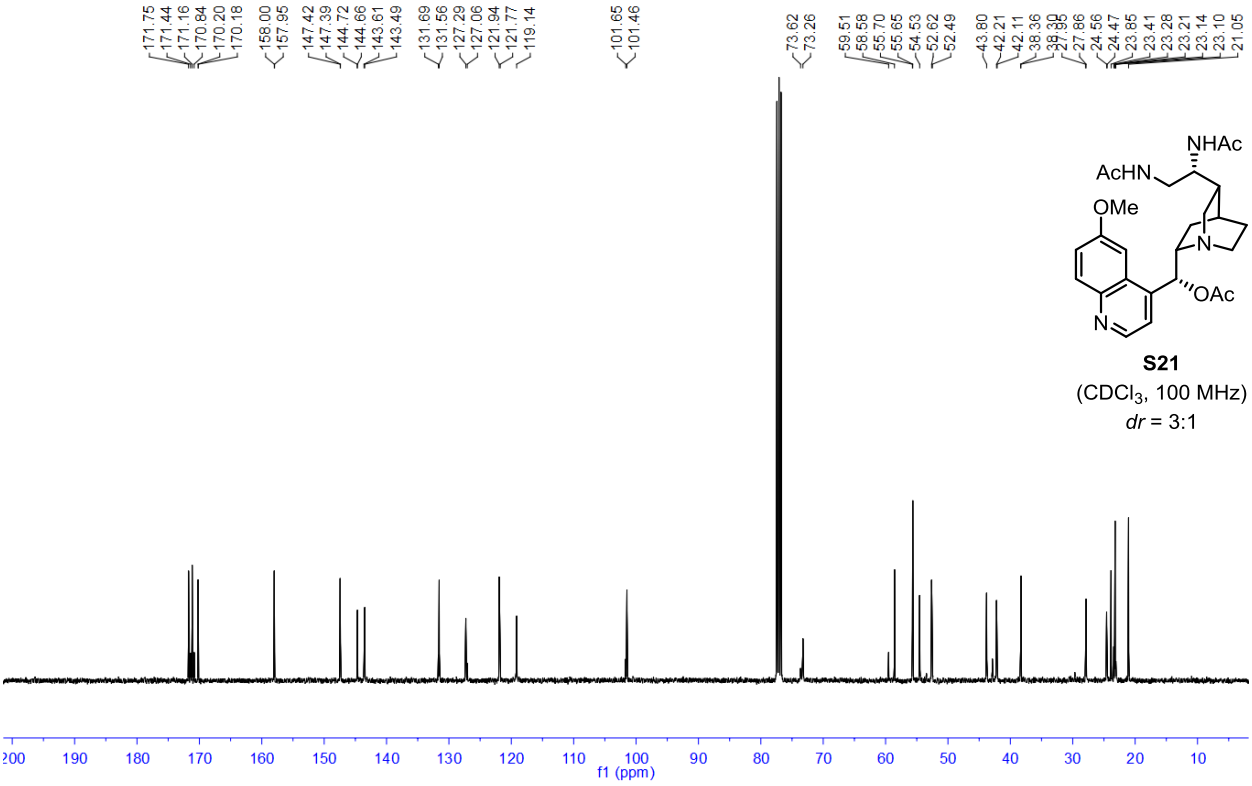
6b
($CDCl_3$, 400 MHz)



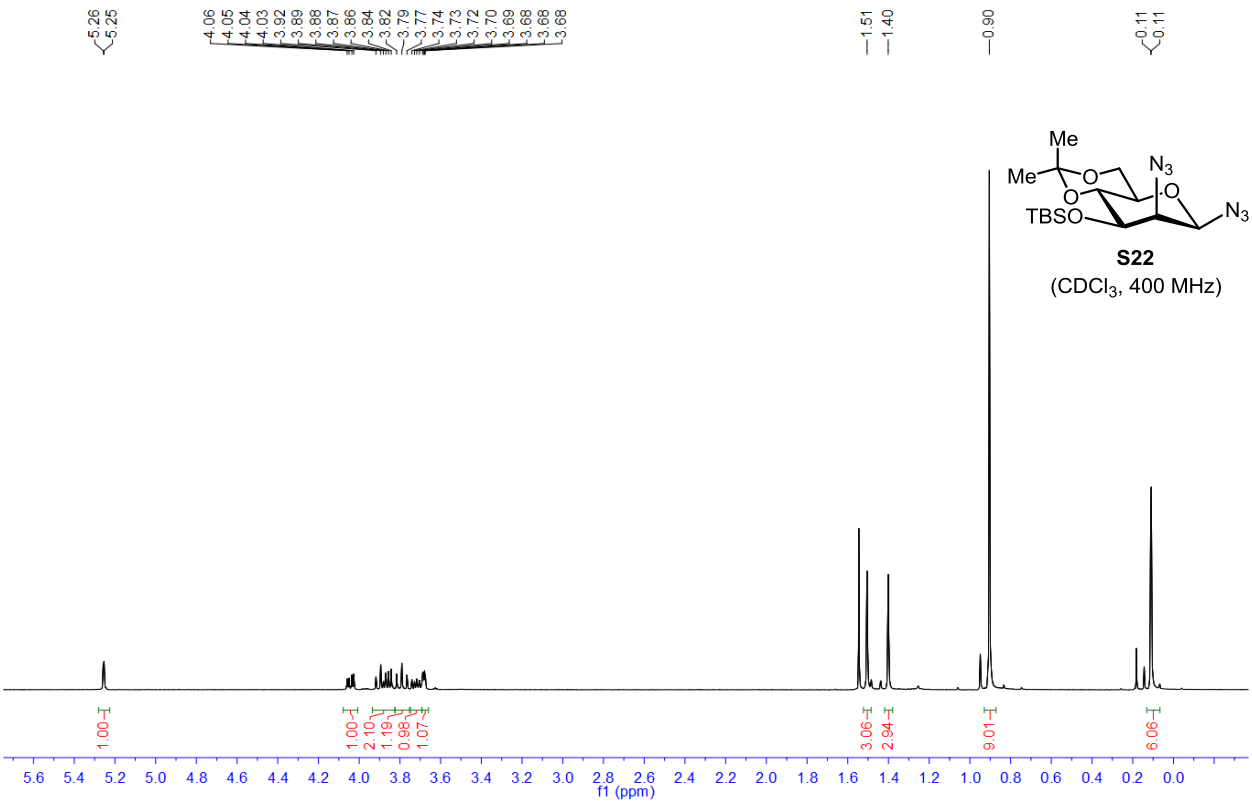
6b
($CDCl_3$, 100 MHz)



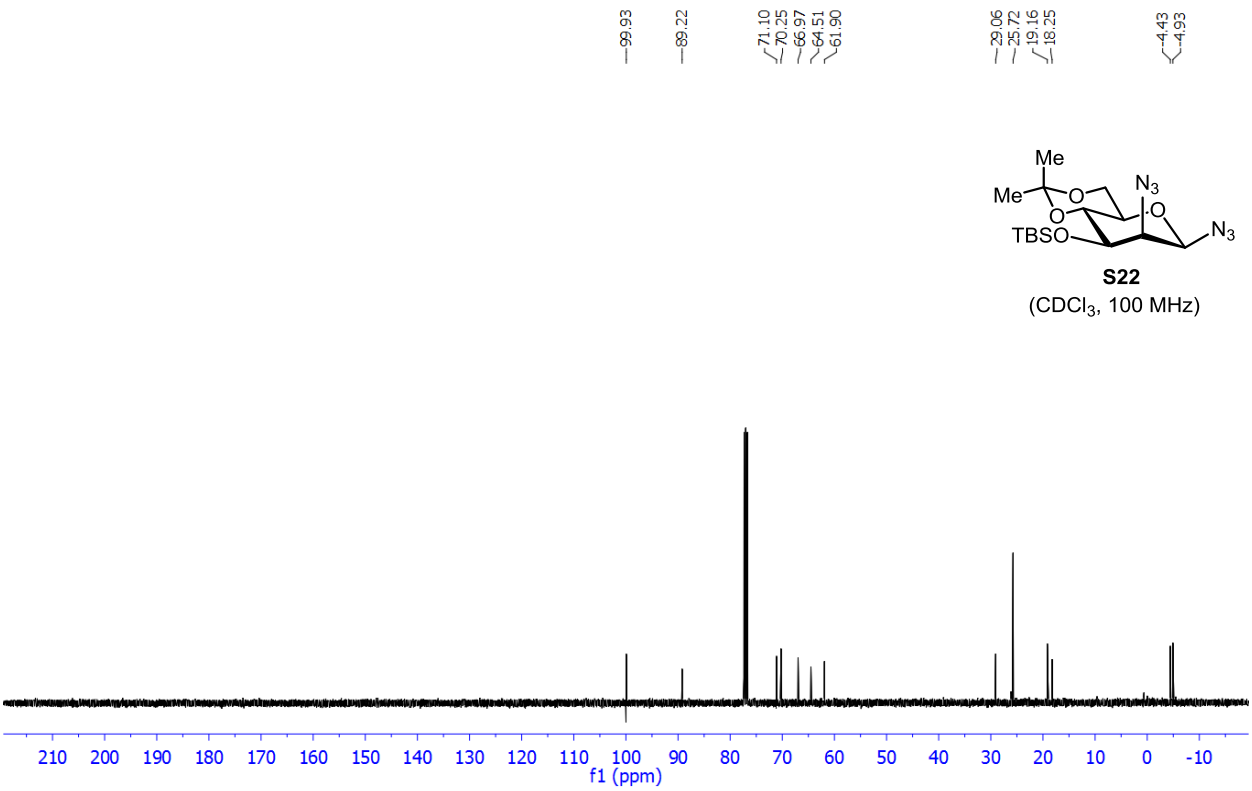
S21
($CDCl_3$, 400 MHz)
dr = 3:1



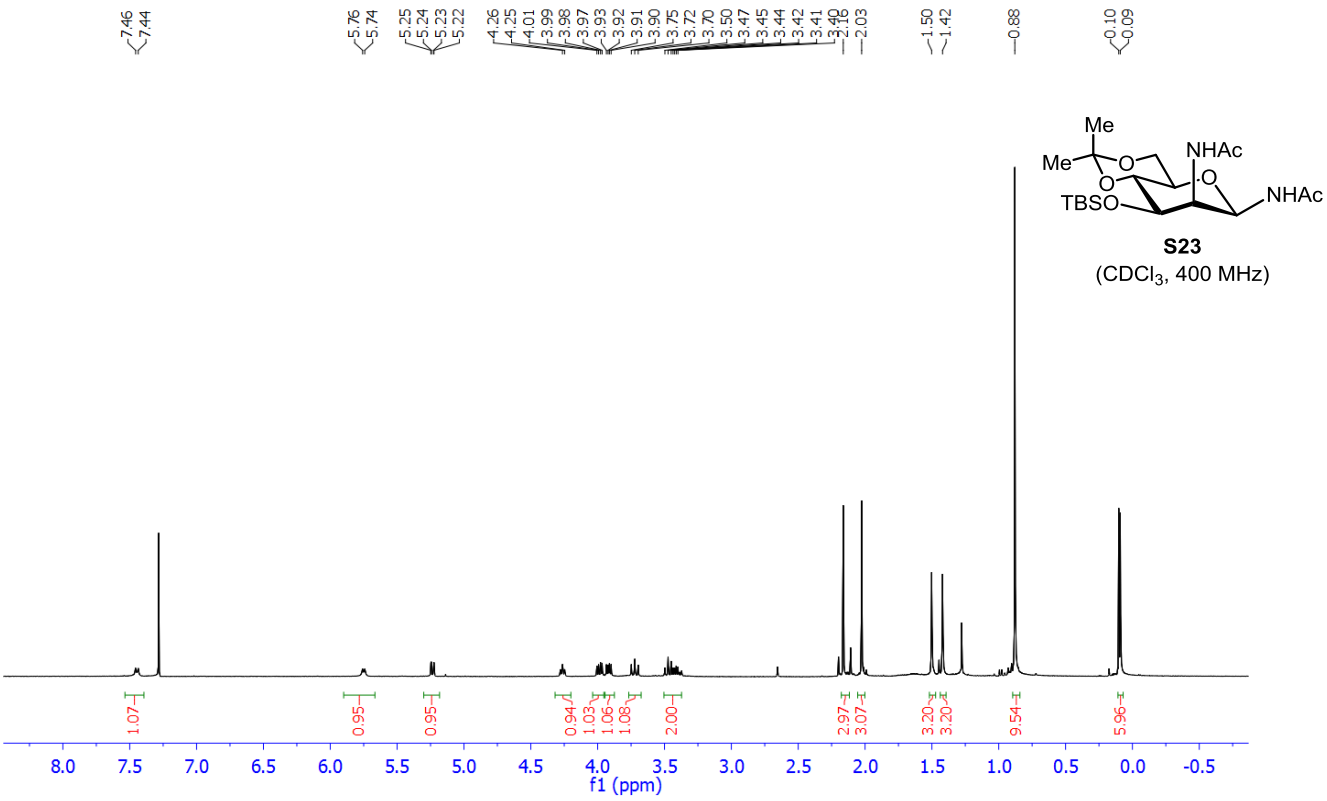
S21
($CDCl_3$, 100 MHz)
dr = 3:1



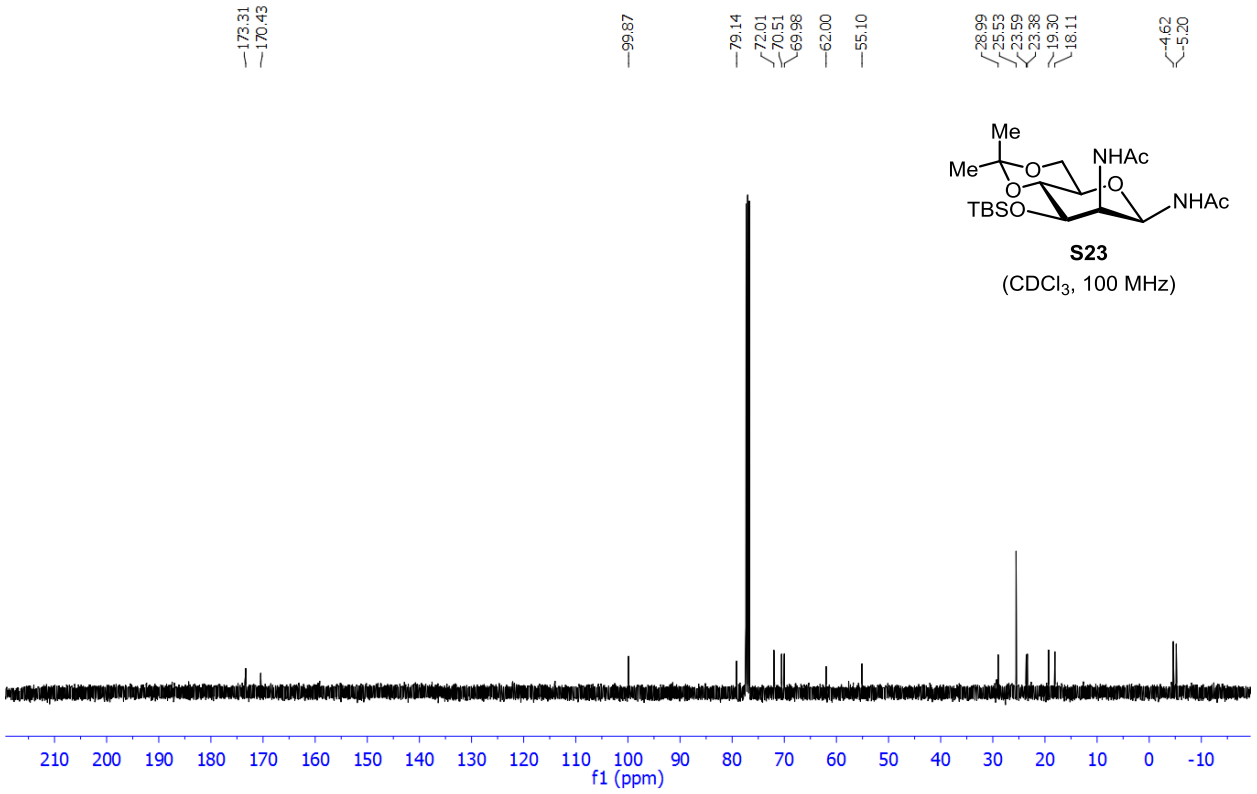
S22
($CDCl_3$, 400 MHz)



S22
($CDCl_3$, 100 MHz)

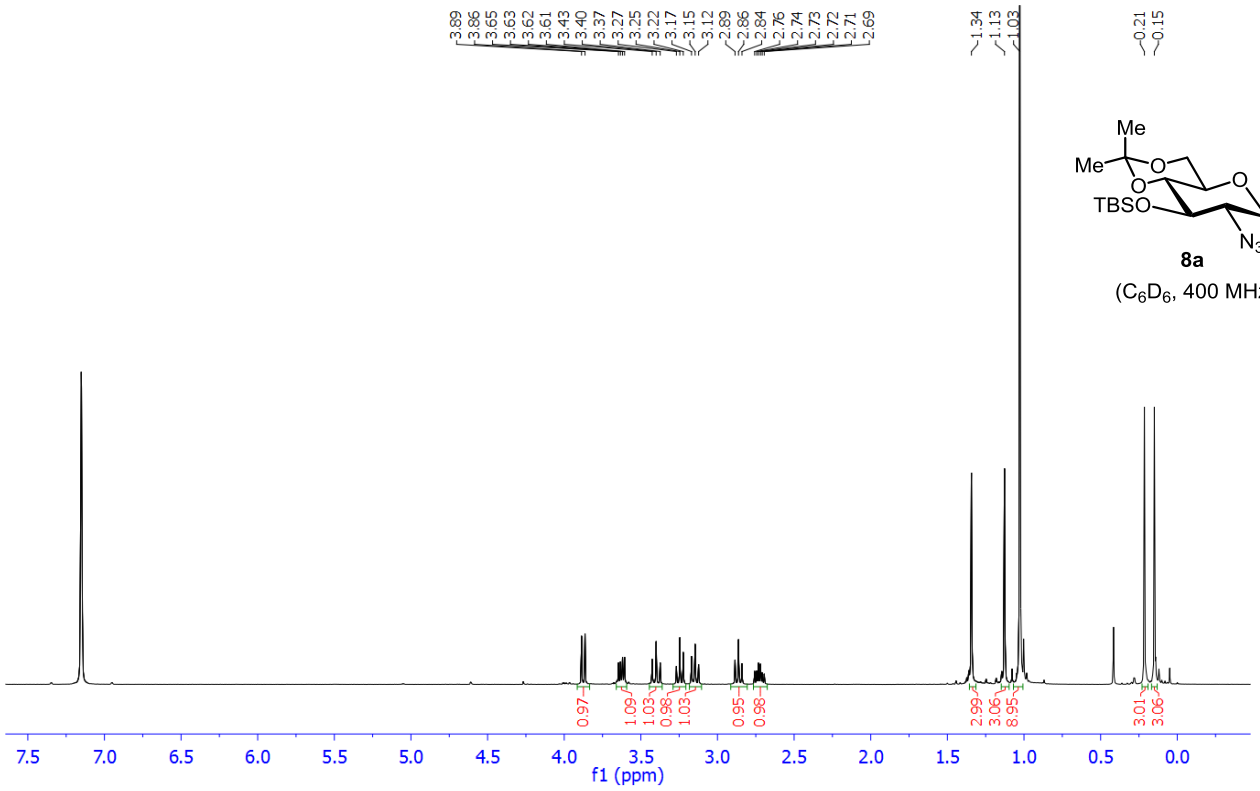


S23
($CDCl_3$, 400 MHz)



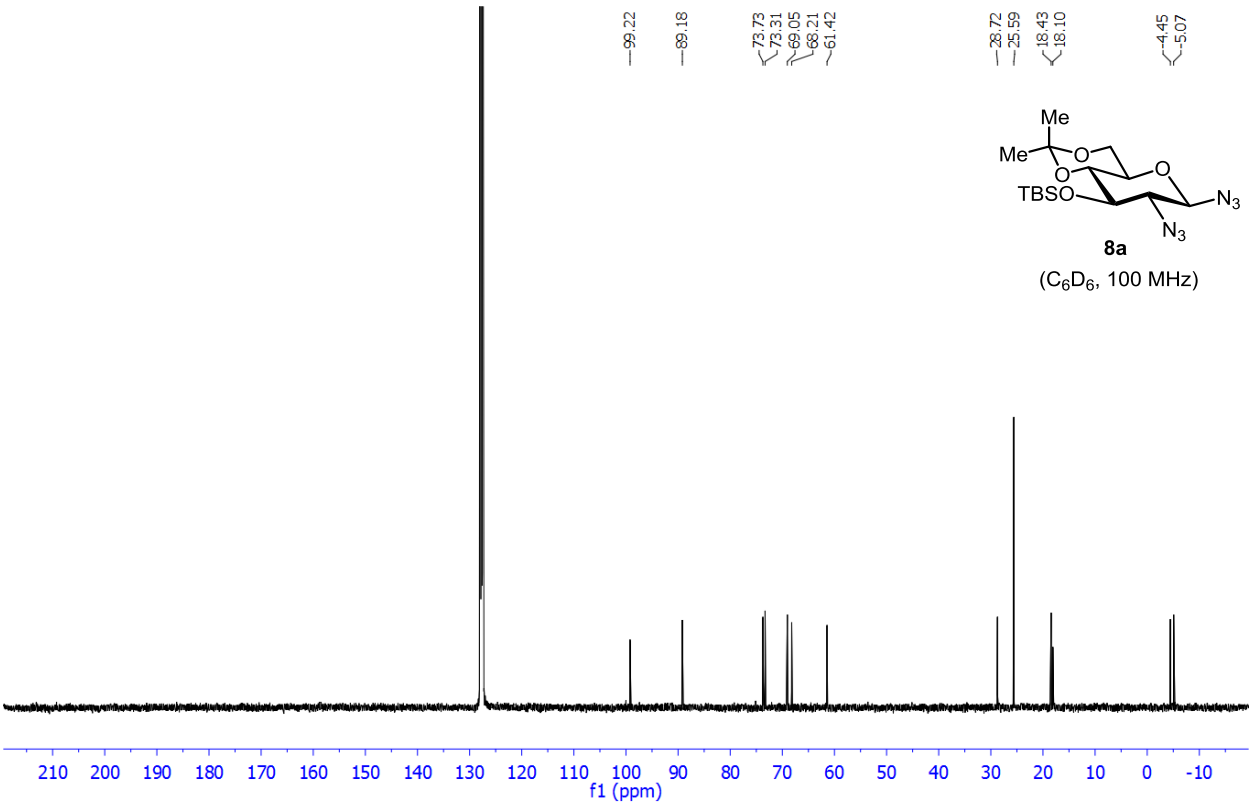
S23

($CDCl_3$, 100 MHz)



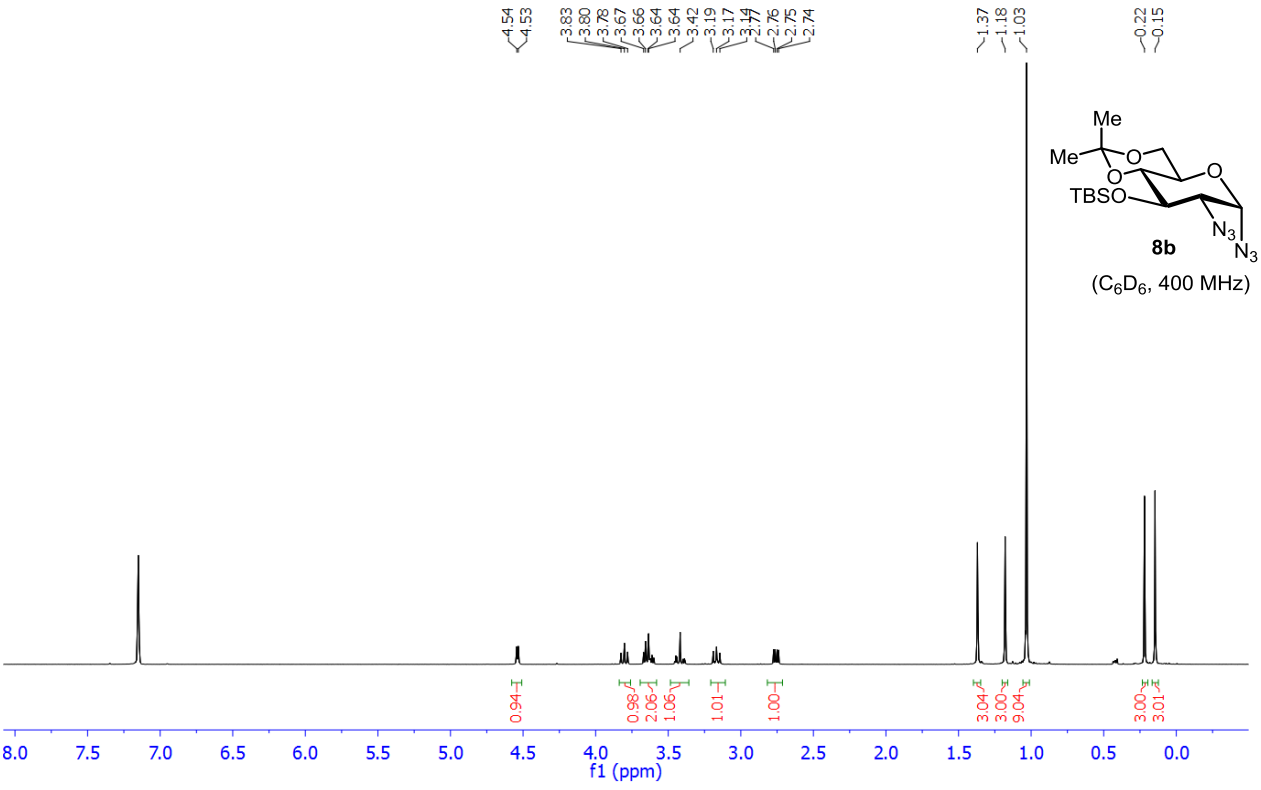
8a

(C_6D_6, 400 MHz)



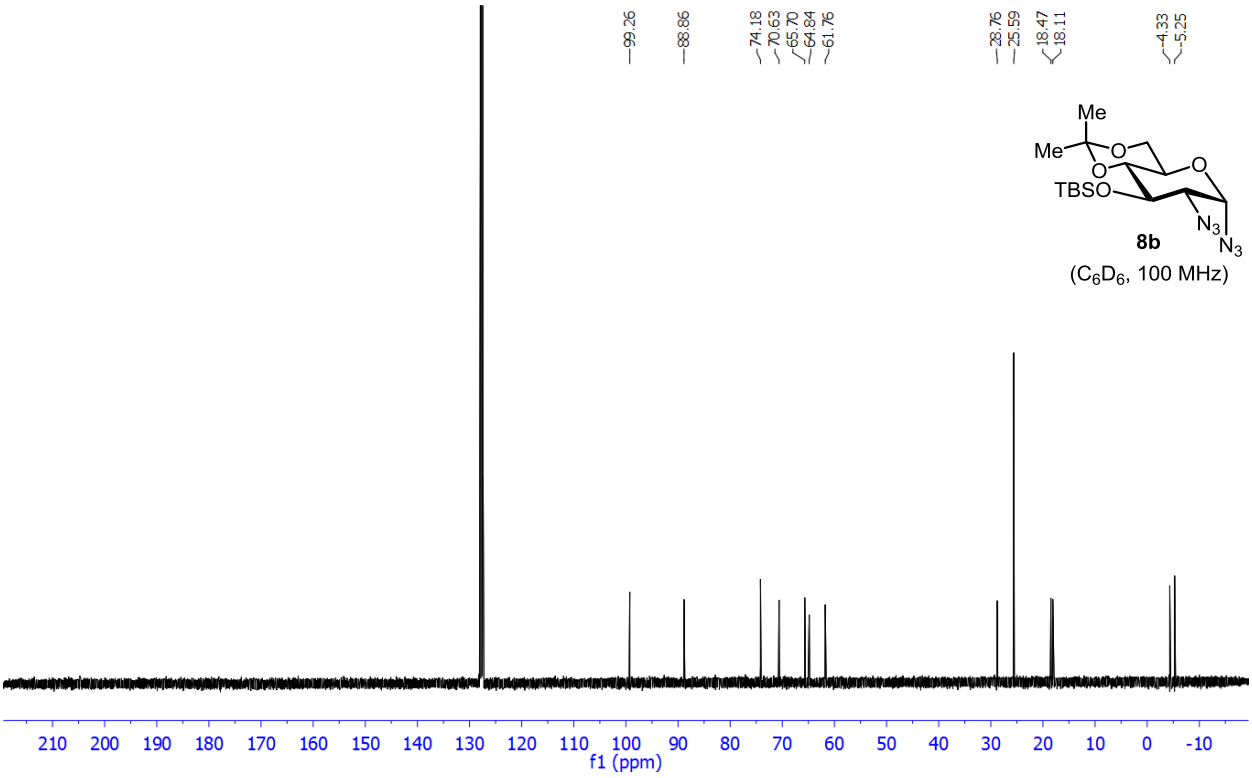
8a

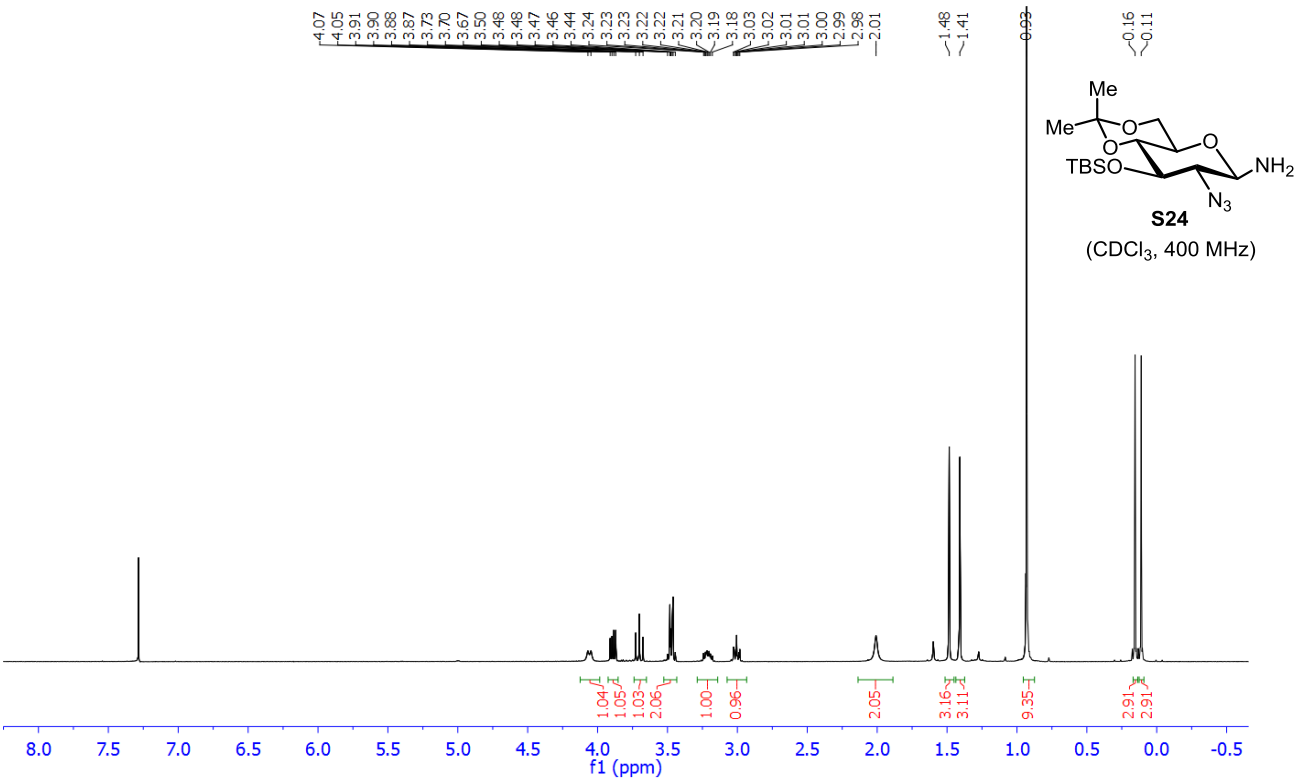
(C_6D_6, 100 MHz)

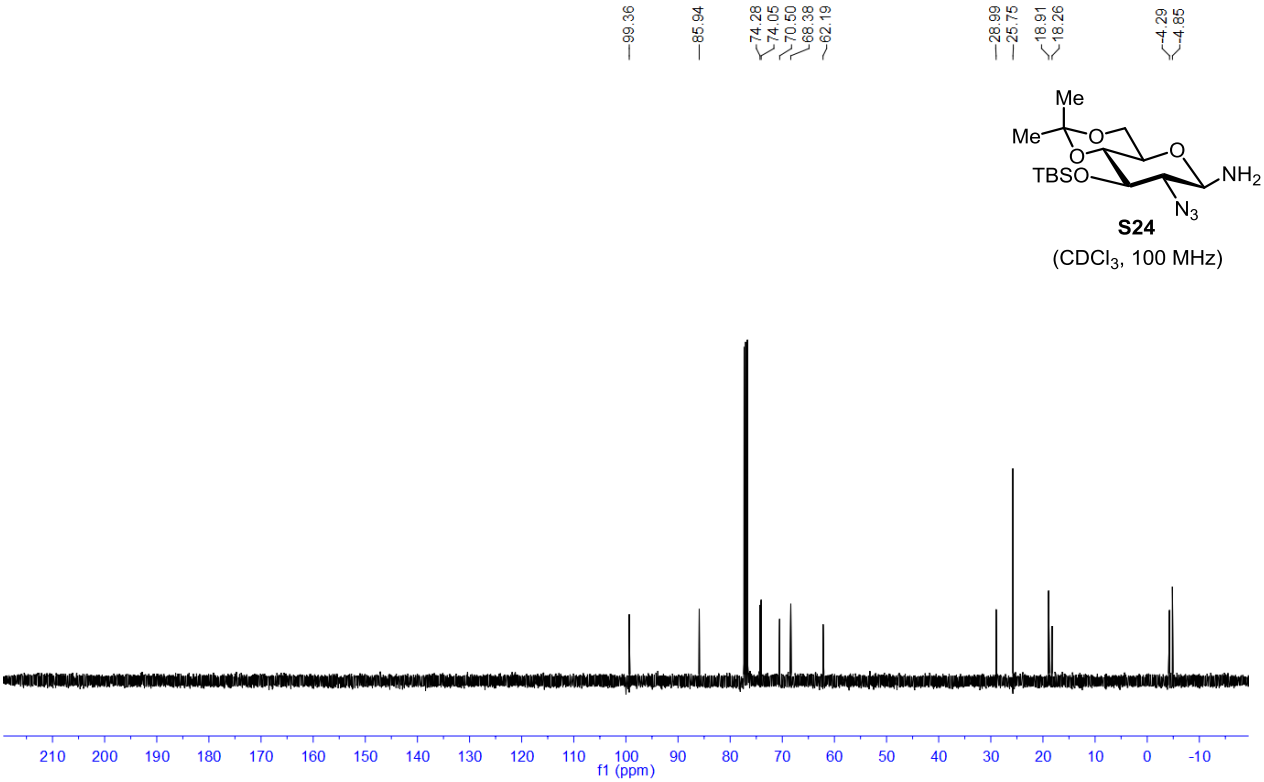


8b

(C_6D_6, 400 MHz)

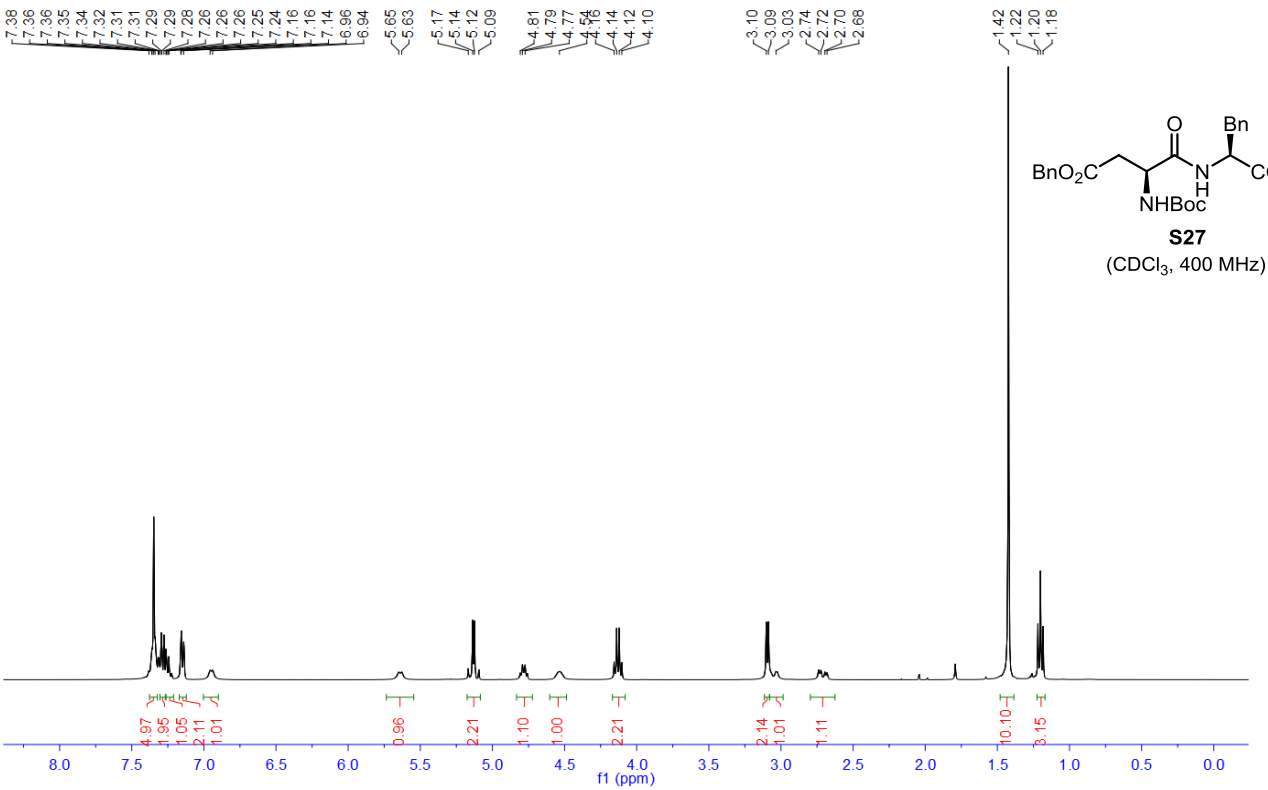

99.26
88.86
74.18
70.63
65.70
64.84
61.76
28.76
25.59
18.47
18.11
-4.33
-5.25
Me
Me
O
O
O
TBSO
N3
N3
8b
(C6D6, 100 MHz)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


4.07
4.05
3.91
3.90
3.88
3.87
3.73
3.70
3.67
3.50
3.48
3.48
3.47
3.46
3.44
3.24
3.23
3.23
3.22
3.22
3.21
3.20
3.19
3.18
3.03
3.02
3.01
3.01
3.00
2.99
2.98
2.01
1.48
1.41
0.93
0.16
0.11
Me
Me
O
O
O
TBSO
NH2
N3
S24
(CDCl3, 400 MHz)
1.04
1.05
1.03
2.06
1.00
0.96
2.05
3.16
3.11
9.35
2.91
2.91
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)



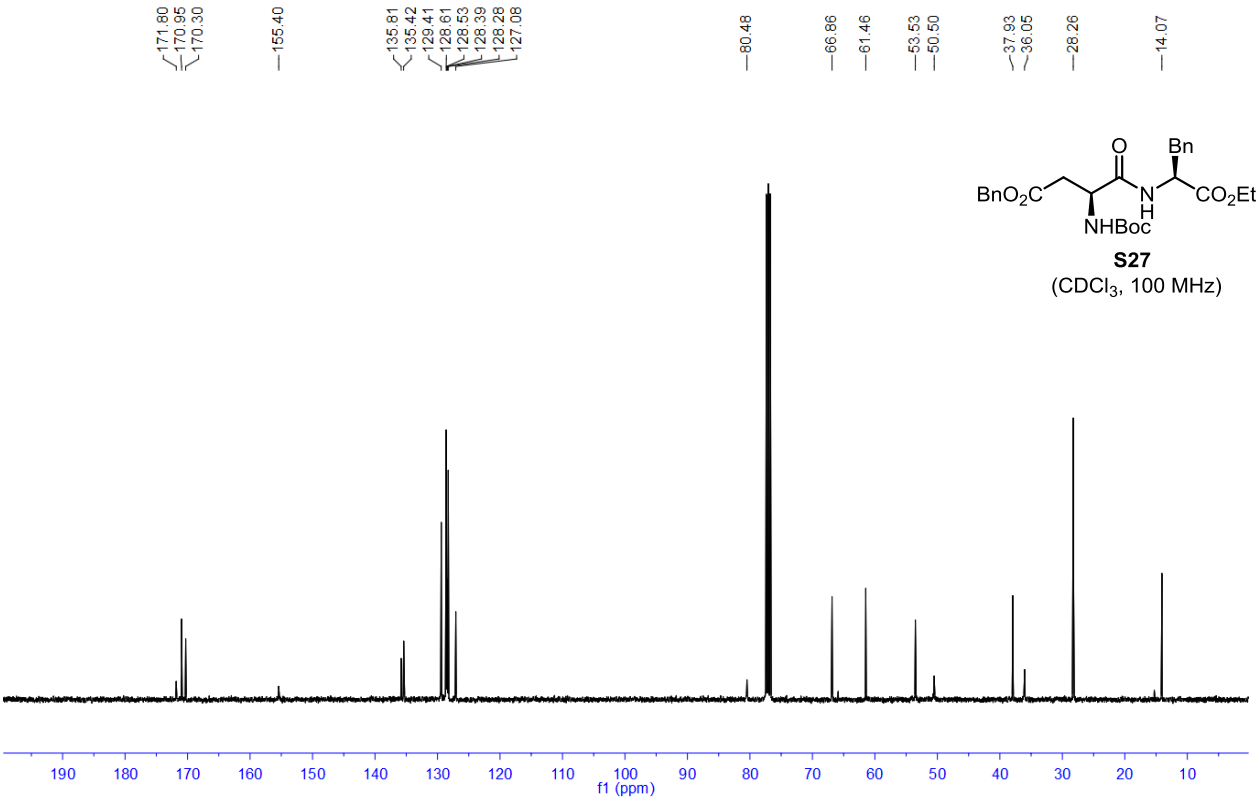
S24

($CDCl_3$, 100 MHz)

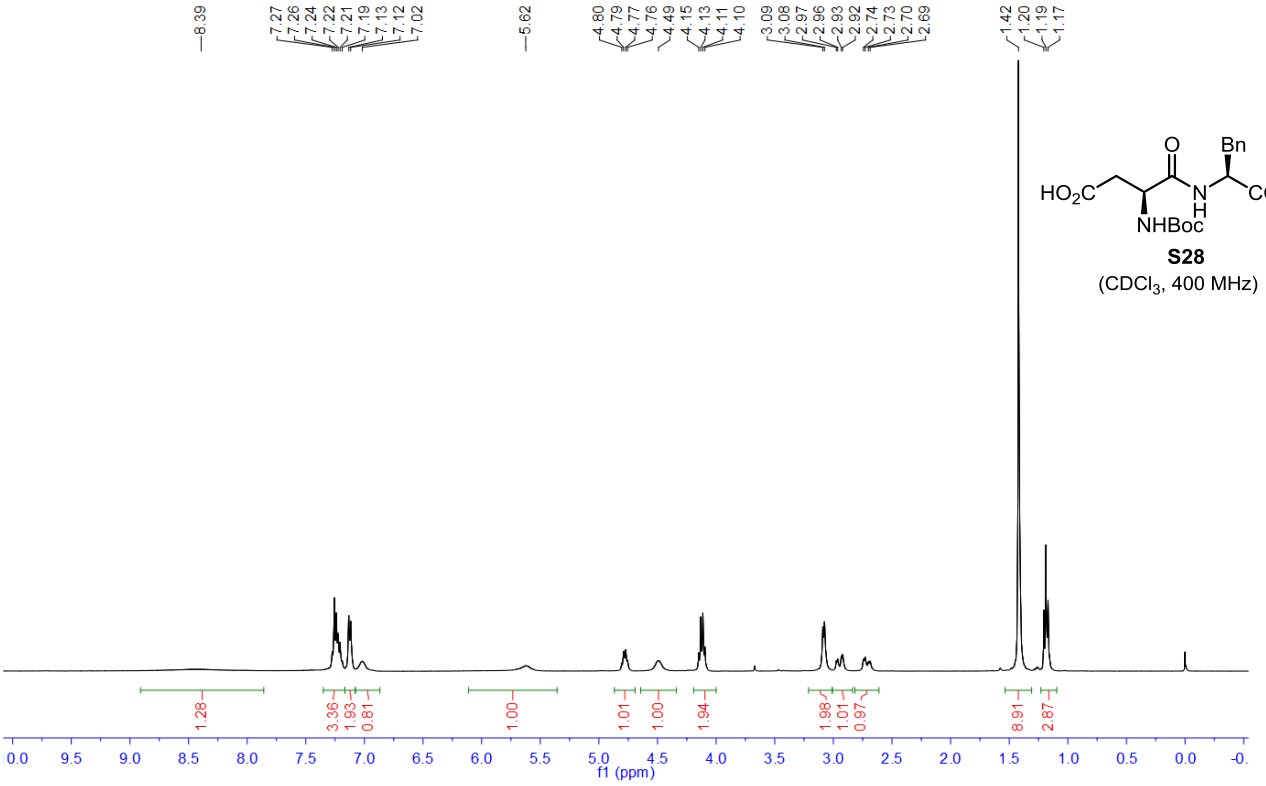


S27

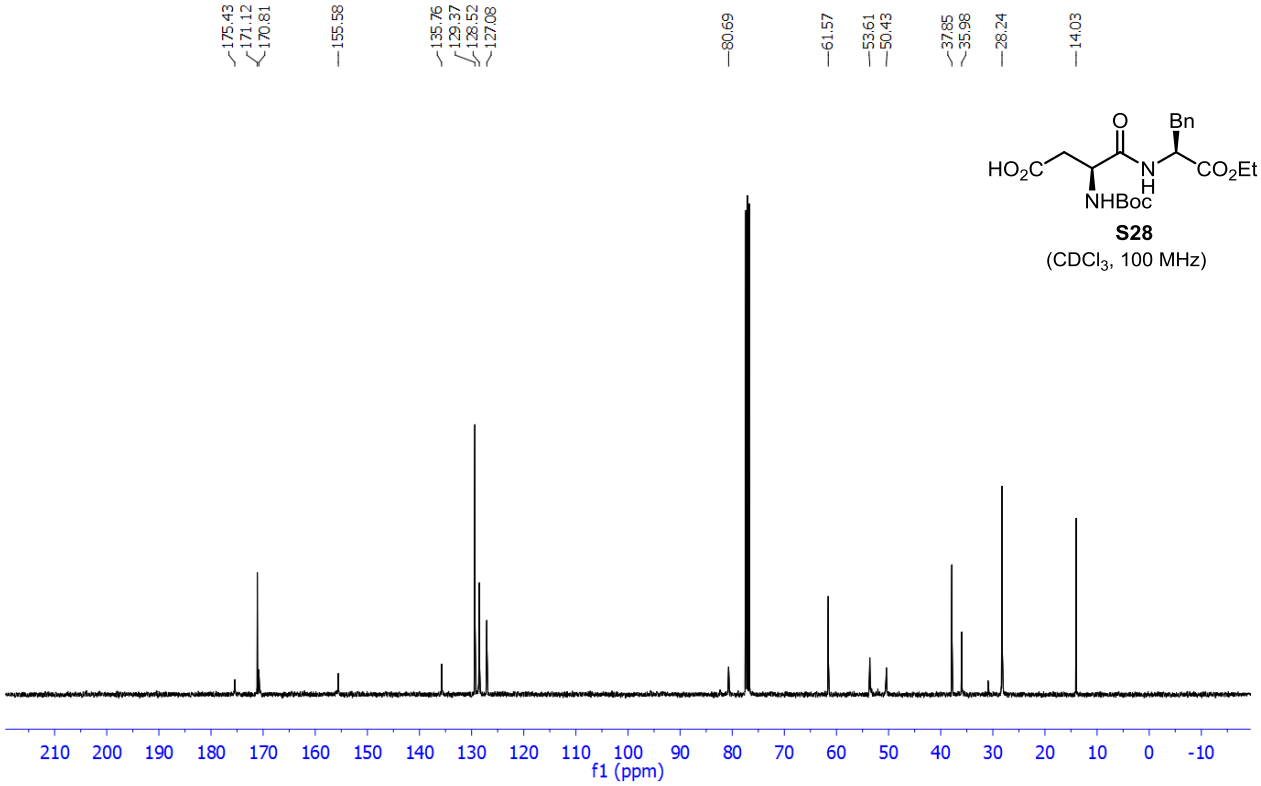
($CDCl_3$, 400 MHz)



S27
($CDCl_3$, 100 MHz)

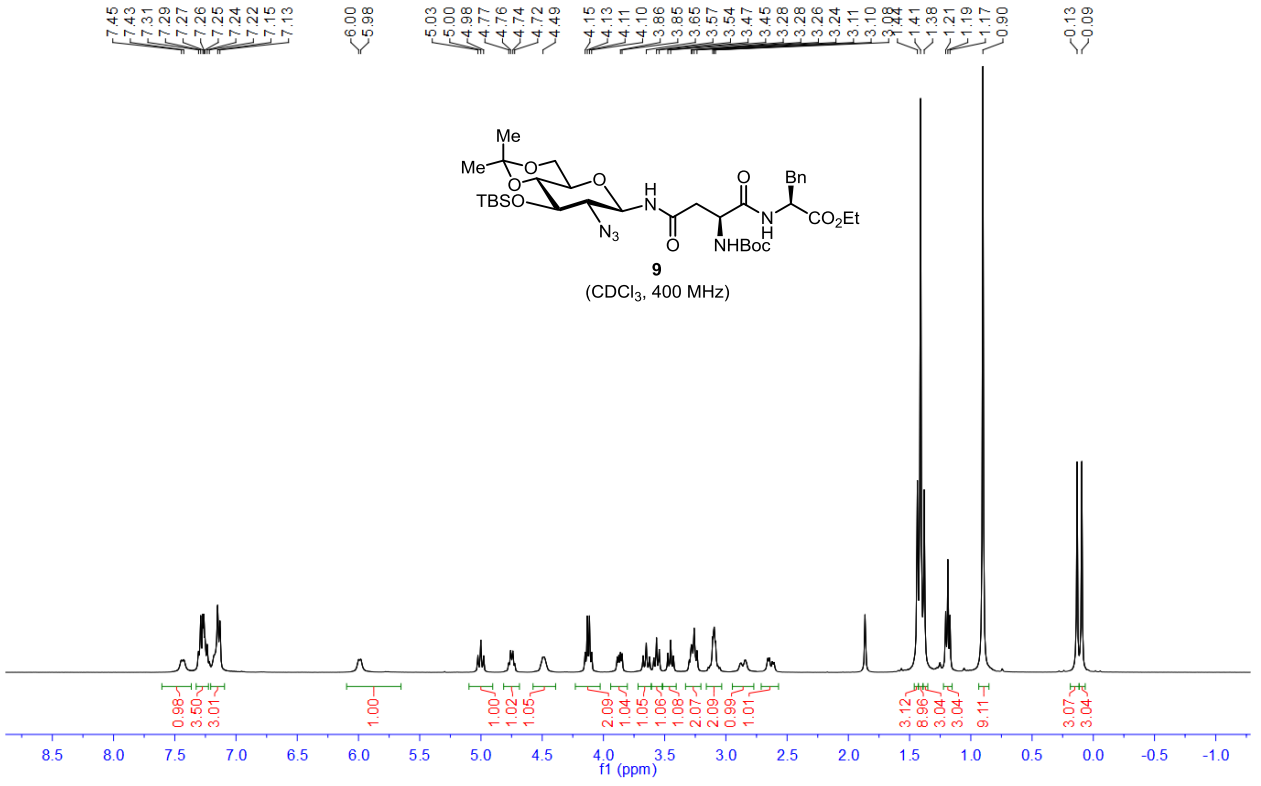


S28
($CDCl_3$, 400 MHz)



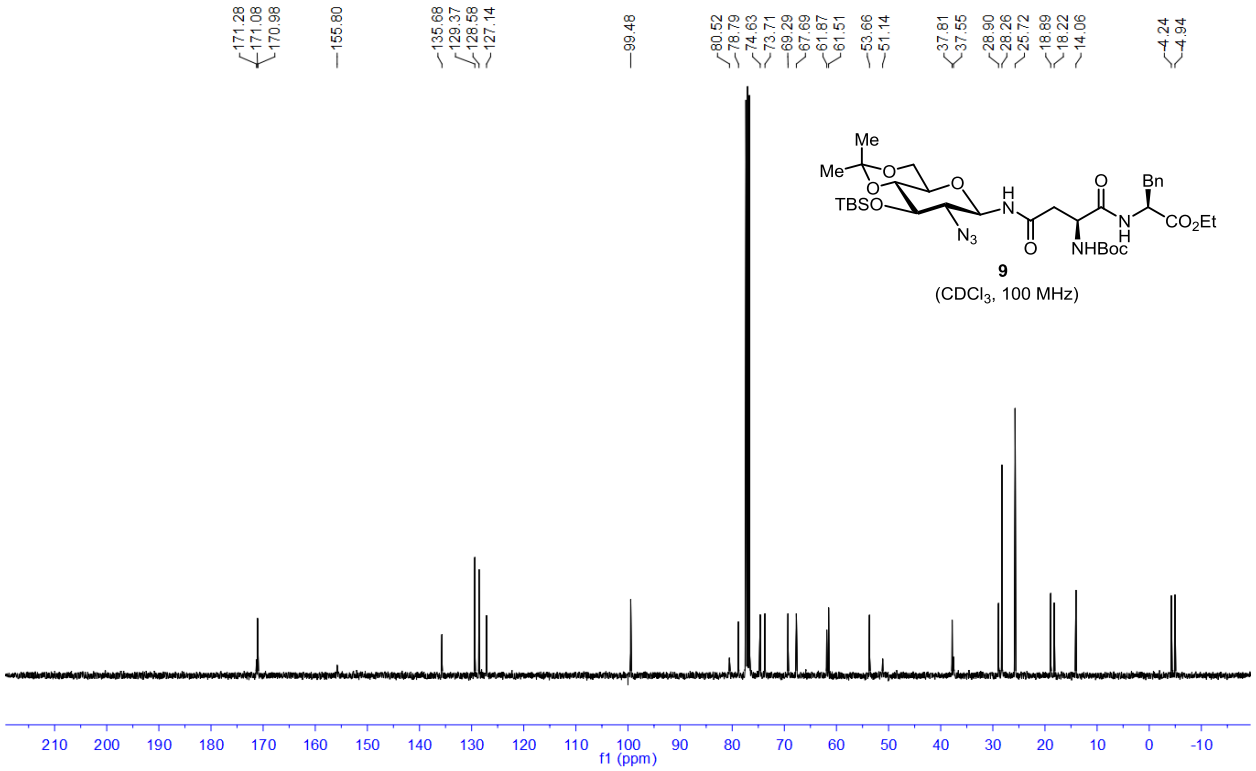
S28

($CDCl_3$, 100 MHz)



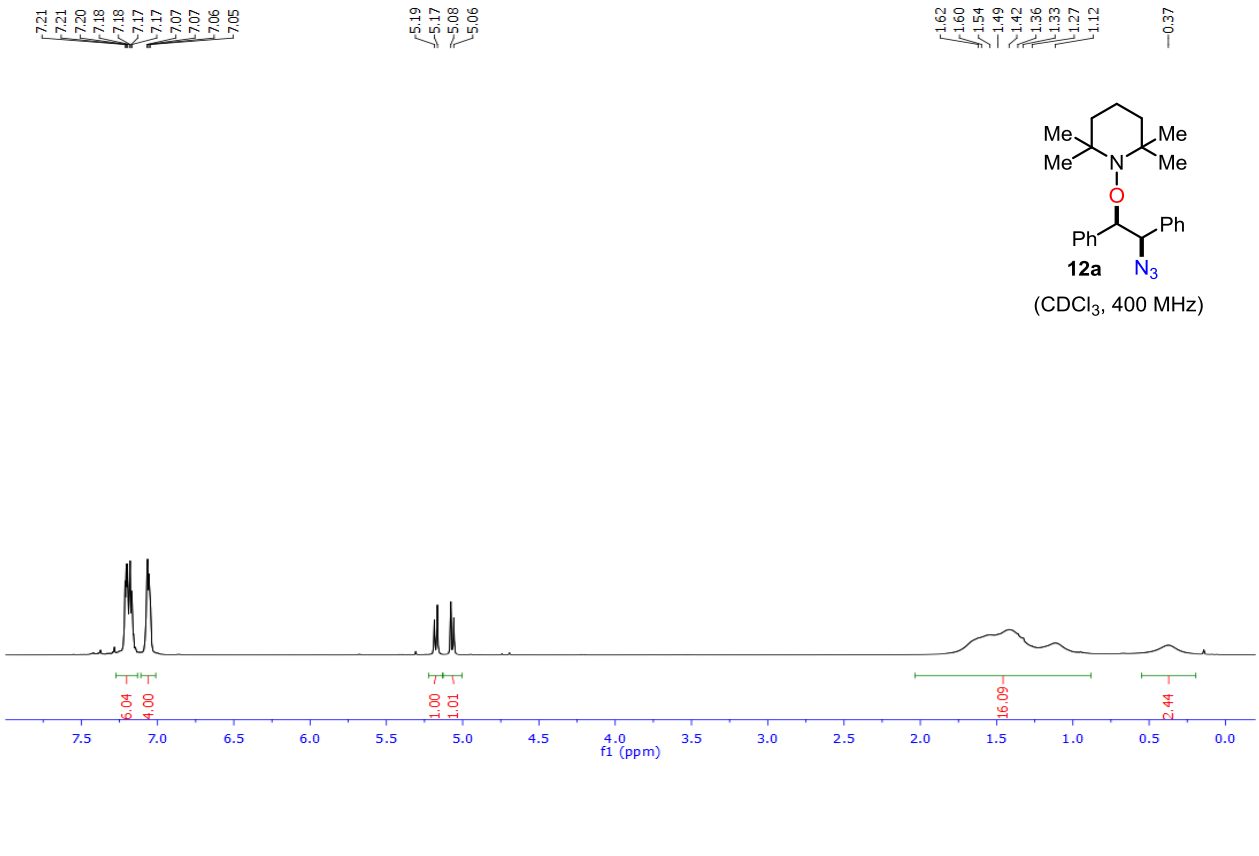
9

($CDCl_3$, 400 MHz)



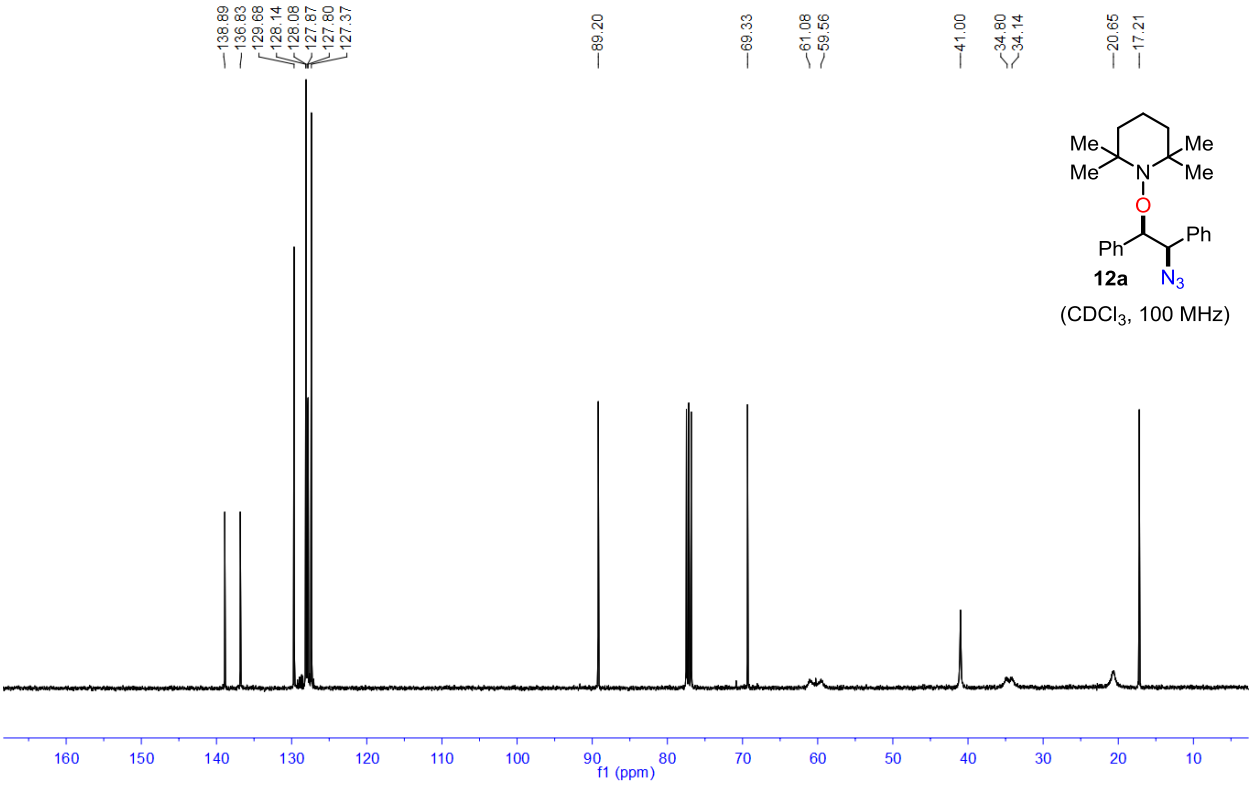
9

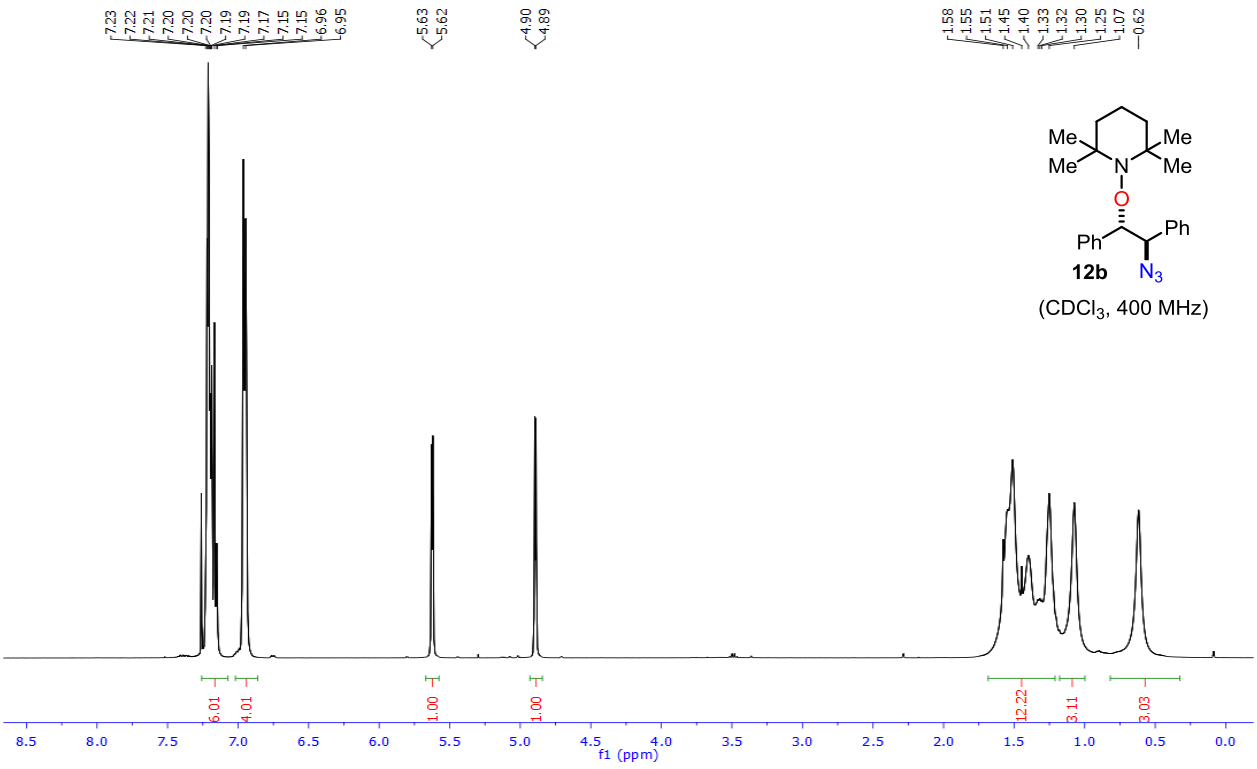
($CDCl_3$, 100 MHz)

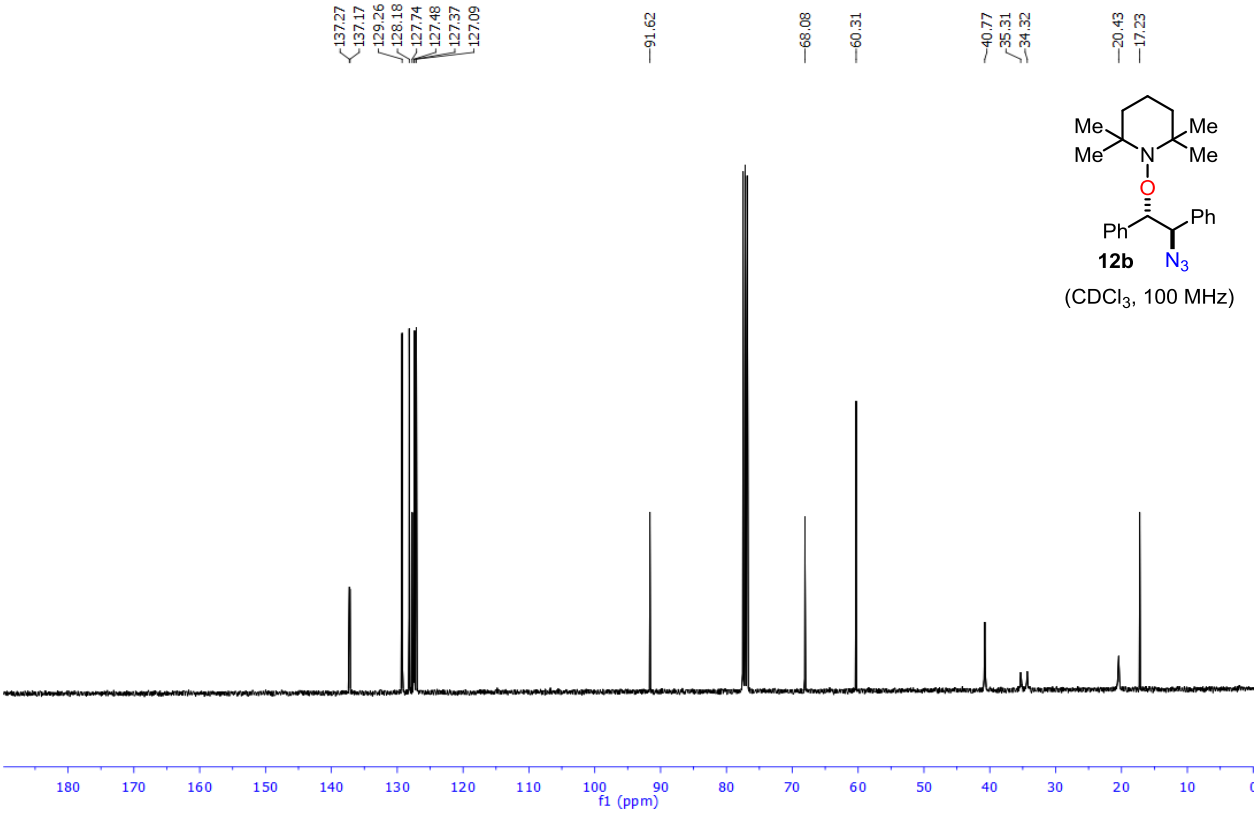


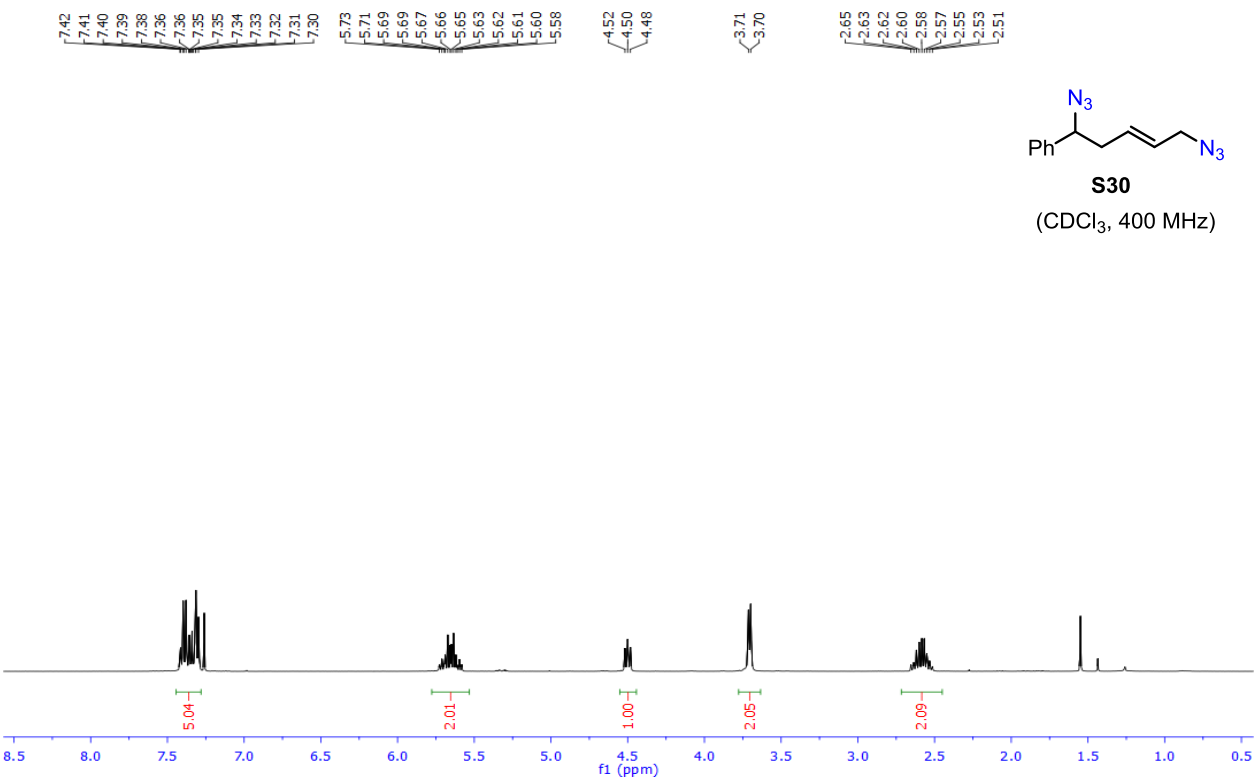
12a

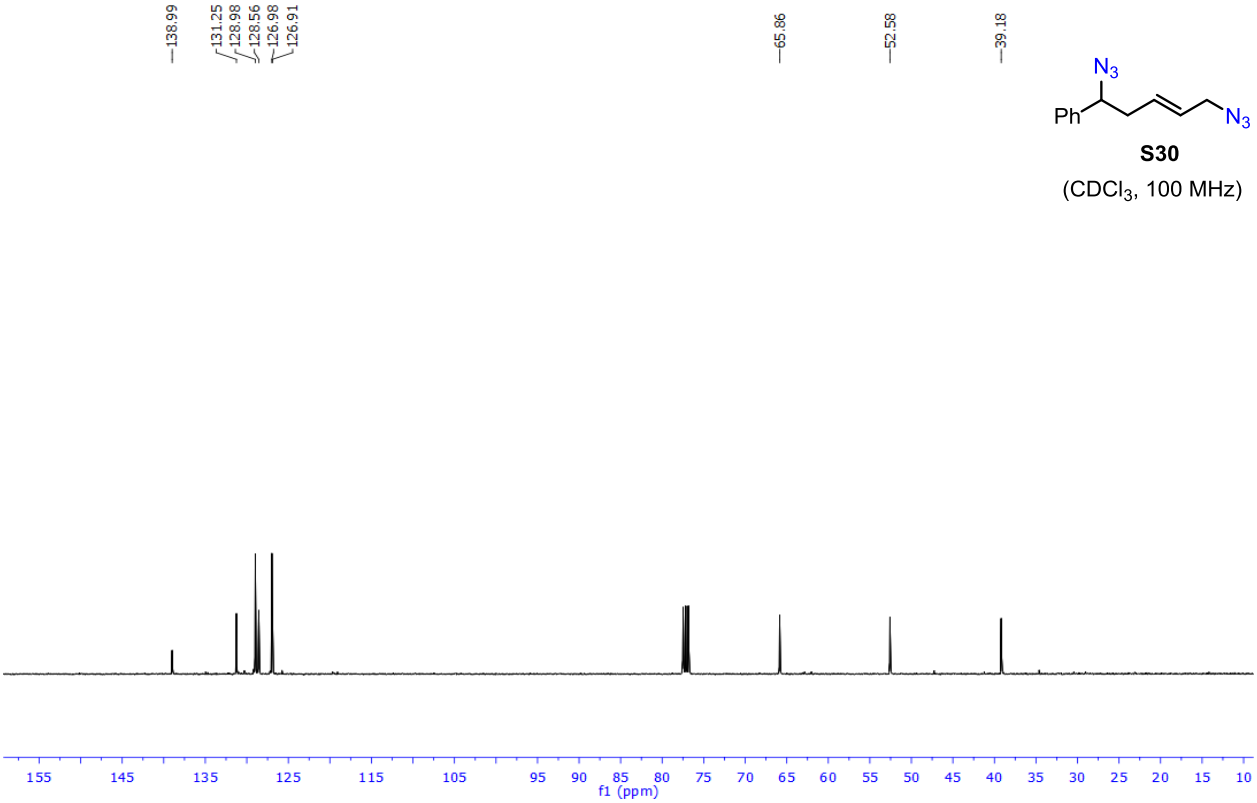
($CDCl_3$, 400 MHz)


138.89
136.83
129.68
128.14
128.08
127.87
127.80
127.37
89.20
69.33
61.08
59.56
41.00
34.80
34.14
20.65
17.21
Me
Me
Me
Me
N
O
Ph
Ph
12a
N3
(CDCl3, 100 MHz)
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


7.23
7.22
7.21
7.20
7.20
7.20
7.19
7.19
7.17
7.15
7.15
6.96
6.95
5.63
5.62
4.90
4.89
1.58
1.55
1.51
1.45
1.40
1.33
1.32
1.30
1.25
1.07
0.62
Me
Me
Me
Me
N
O
Ph
Ph
12b
N3
(CDCl3, 400 MHz)
6.01
4.01
1.00
1.00
12.22
3.11
3.03
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

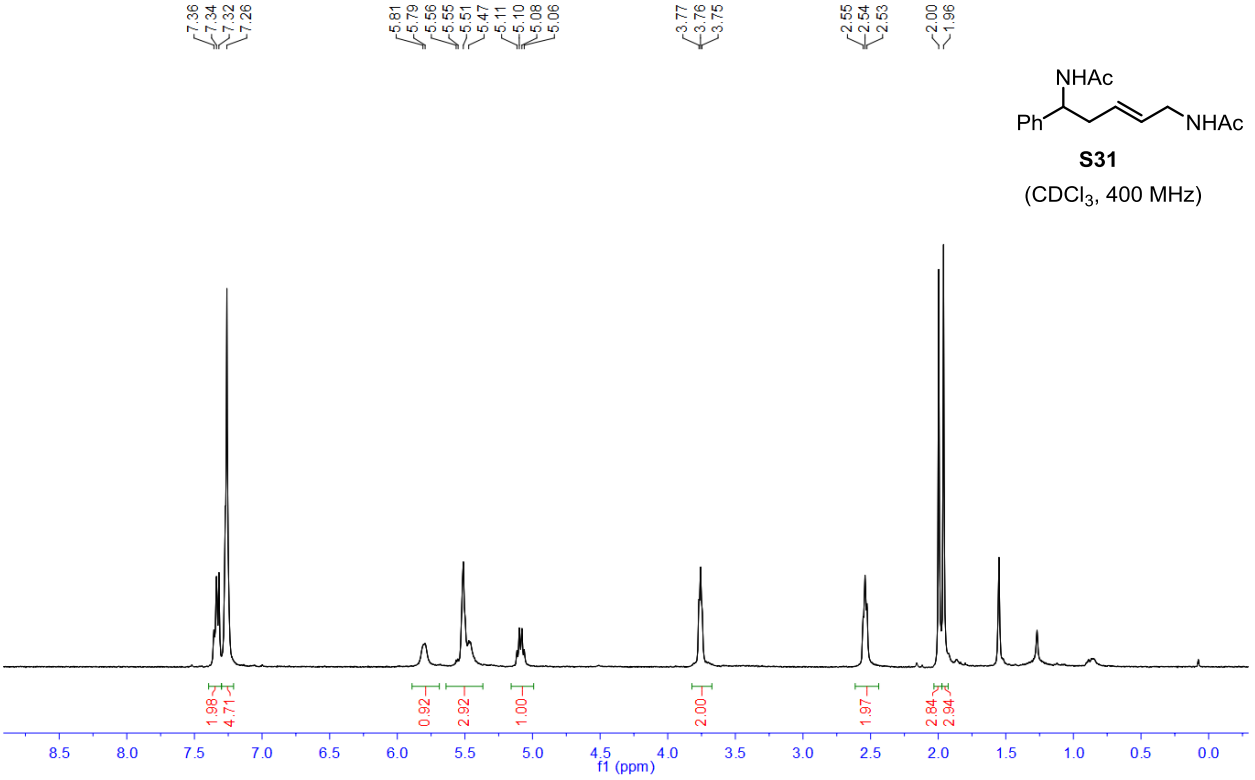

137.27
137.17
129.26
128.18
127.74
127.48
127.37
127.09
91.62
68.08
60.31
40.77
35.31
34.32
20.43
17.23
Me
Me
Me
Me
N
O
Ph
Ph
N3
12b
(CDCl3, 100 MHz)
f1 (ppm)


7.42
7.41
7.40
7.39
7.38
7.36
7.36
7.35
7.35
7.34
7.33
7.32
7.31
7.30
5.73
5.71
5.69
5.69
5.67
5.66
5.65
5.63
5.62
5.61
5.60
5.58
4.52
4.50
4.48
3.71
3.70
2.65
2.63
2.62
2.60
2.58
2.57
2.55
2.53
2.51
N3
Ph
N3
S30
(CDCl3, 400 MHz)
5.04
2.01
1.00
2.05
2.09
f1 (ppm)



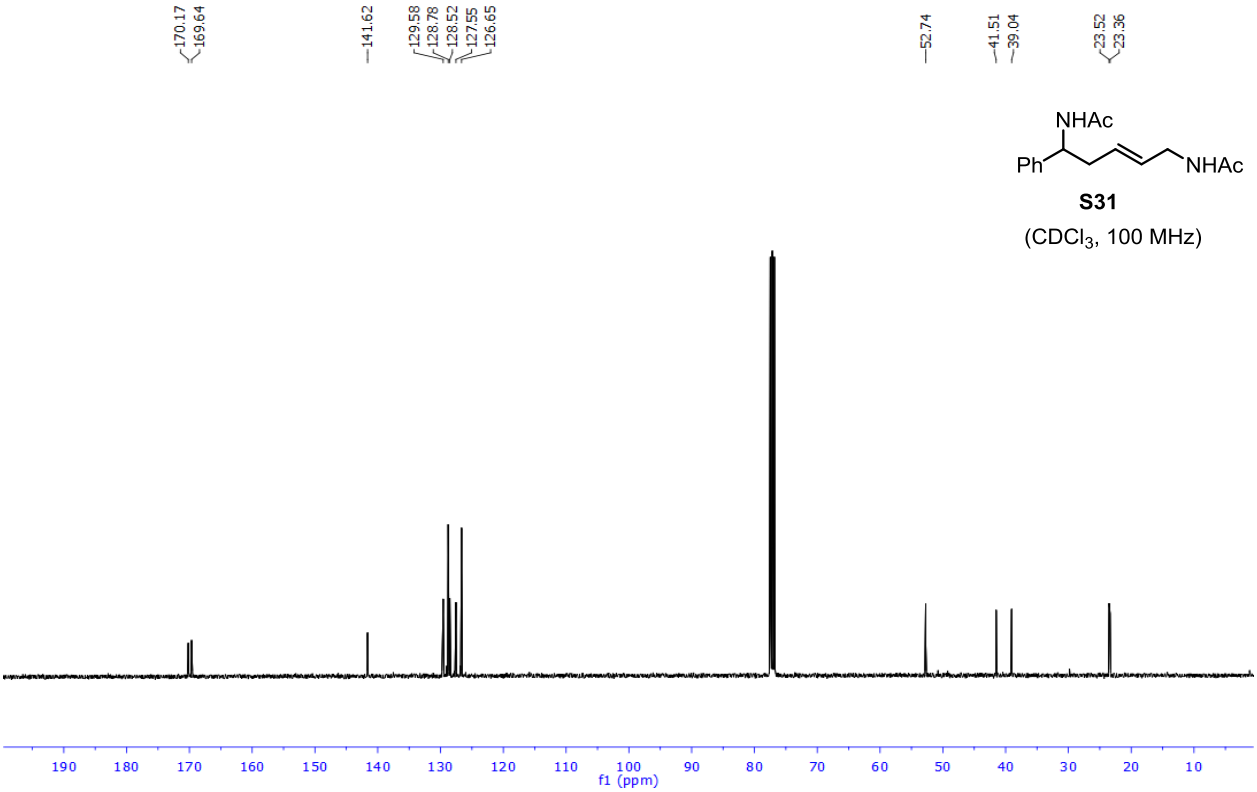
S30

($CDCl_3$, 100 MHz)



S31

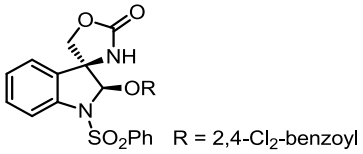
($CDCl_3$, 400 MHz)



S31

($CDCl_3$, 100 MHz)

Appendix E X-ray Crystallographic Analysis for Product Absolute Stereochemistry Determination



2

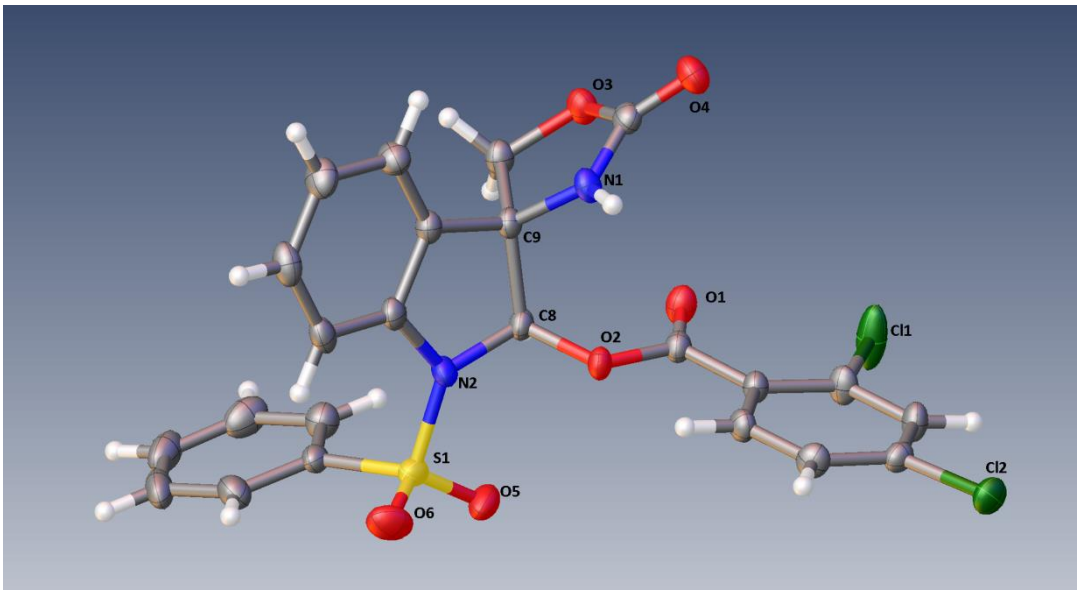


Table 1. Crystal data and structure refinement for B302_0m

Identification code	B302_0m
Empirical formula	$C_{26}H_{22}Cl_2N_2O_7S$
Formula weight	577.41
Temperature/K	173(2)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	9.6790(7)
b/Å	11.8883(8)
c/Å	22.4824(16)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2587.0(3)
Z	4

ρ_{calc}mg/mm^3	1.483
m/mm^{-1}	0.382
F(000)	1192.0
Crystal size/mm^3	0.698 × 0.309 × 0.23
2Θ range for data collection	3.624 to 61.158°
Index ranges	$-13 \leq h \leq 13$, $-16 \leq k \leq 17$, $-28 \leq l \leq 32$
Reflections collected	20608
Independent reflections	7834[R(int) = 0.0289]
Data/restraints/parameters	7834/1/349
Goodness-of-fit on F^2	1.033
Final R indexes [I>=2σ (I)]	R_1 = 0.0482, wR_2 = 0.1153
Final R indexes [all data]	R_1 = 0.0572, wR_2 = 0.1218
Largest diff. peak/hole / e Å^{-3}	0.77/-0.42
Flack parameter	0.012(18)

Table 2. Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for B302_0m. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	***x***	***y***	***z***	**U(eq)**
S1	-3467.1(8)	-6310.7(7)	-3791.5(3)	28.52(17)
Cl2	-2358.9(8)	-7597.4(6)	-7753.5(3)	31.40(17)
Cl1	-4886.0(12)	-4143.1(9)	-6739.3(4)	53.7(3)
O2	-2651(2)	-5279.5(17)	-5088.2(8)	23.5(4)
O3	-2056(2)	-1889.3(19)	-4968.4(9)	28.9(5)
O1	-3946(2)	-3947.3(19)	-5525.3(9)	29.7(5)
O5	-4628(3)	-6284(2)	-4184.8(10)	40.3(6)
O4	-792(2)	-2090(2)	-5804.8(10)	34.5(5)
N2	-2383(3)	-5384(2)	-4066(1)	27.1(5)
O7	-8934(3)	-5021(2)	-5587.2(10)	40.0(6)
O6	-2724(3)	-7335(2)	-3698.5(12)	45.2(6)
N1	-957(2)	-3498(2)	-5107(1)	23.9(5)
C3	-2683(3)	-6833(2)	-7111.8(12)	23.2(5)
C18	-3989(3)	-5812(3)	-3090.3(12)	25.3(6)
C7	-3316(3)	-4817(3)	-5560.3(12)	22.8(5)
C5	-3802(3)	-5279(3)	-6640.2(13)	26.9(6)
C12	-603(3)	-4115(2)	-4071.7(12)	21.9(5)
C9	-1605(3)	-3683(2)	-4536.0(11)	20.4(5)

C10	-1211(3)	-2469(3)	-5338.1(12)	24.9(5)
C2	-2018(3)	-7107(3)	-6588.1(13)	26.6(6)
C4	-3595(3)	-5943(3)	-7143.1(12)	27.8(6)
C6	-3138(3)	-5526(2)	-6103.0(11)	21.5(5)
C8	-2747(3)	-4623(2)	-4547.3(11)	22.3(5)
C17	-1075(3)	-5103(2)	-3815.8(12)	23.1(5)
C1	-2246(3)	-6452(2)	-6090.2(12)	24.1(5)
C16	-302(3)	-5688(3)	-3401.4(12)	27.2(6)
C25	-8230(4)	-5681(3)	-5311.6(15)	35.2(7)
C11	-2185(3)	-2489(3)	-4413.8(12)	25.4(5)
C19	-3594(4)	-6395(3)	-2582.7(14)	34.3(7)
C13	669(3)	-3674(3)	-3923.5(13)	28.4(6)
C23	-4869(3)	-4895(3)	-3062.9(14)	32.8(7)
C22	-5364(4)	-4565(4)	-2508.7(17)	42.0(8)
C14	1459(3)	-4242(3)	-3500.4(14)	33.0(7)
C15	984(3)	-5227(3)	-3248.0(13)	31.6(6)
C20	-4123(4)	-6055(4)	-2038.0(14)	44.3(9)
C21	-5009(4)	-5152(4)	-2003.5(15)	45.2(10)
C26	-8877(6)	-6438(4)	-4858.2(18)	57.9(12)
C24	-6713(4)	-5759(4)	-5408(2)	60.1(13)

Table 3. Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for B302_0m. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+...+2hka \times b \times U_{12}]$

Atom	**U_{11}**	**U_{22}**	**U_{33}**	**U_{23}**	**U_{13}**	**U_{12}**
S1	38.2(4)	26.5(4)	20.8(3)	-3.5(3)	4.5(3)	-10.9(3)
Cl2	38.6(4)	29.8(4)	25.8(3)	-9.0(3)	2.2(3)	1.1(3)
Cl1	74.9(6)	58.7(6)	27.5(4)	-11.9(4)	-17.4(4)	45.3(5)
O2	30.3(9)	26(1)	14.3(8)	-0.9(7)	-1.8(7)	0.1(8)
O3	37.8(11)	25.4(11)	23.5(10)	2.8(8)	-0.9(8)	4.7(9)
O1	34.7(10)	30.6(12)	23.9(10)	-3.8(8)	-2.7(8)	7.2(9)
O5	45.3(13)	52.5(16)	23(1)	-4.4(11)	-0.4(9)	-23.7(12)
O4	42.0(12)	35.7(13)	25.8(10)	8.8(9)	1.4(9)	-1.7(10)
N2	31.1(12)	34.1(13)	16.1(10)	4.7(9)	0.9(9)	-11.1(11)
O7	44.2(13)	45.6(15)	30.4(12)	-5.8(10)	-6.4(10)	15.7(12)
O6	63.2(16)	24.5(11)	48.0(15)	-5(1)	13.3(13)	-3.9(11)
N1	25.1(11)	29.1(13)	17.4(10)	2.5(9)	4.2(8)	2.1(9)
C3	25.2(12)	23.8(13)	20.6(12)	-5.2(10)	1.8(10)	-1.2(11)

C18	31.0(13)	28.0(14)	16.9(11)	-0.7(10)	2.8(10)	-9.9(11)
C7	23.9(12)	27.4(14)	17.1(11)	-0.6(10)	-0.5(9)	-1.6(10)
C5	30.9(13)	27.0(14)	22.8(13)	0.5(11)	-4.0(11)	12.1(11)
C12	23.8(12)	24.8(13)	17.2(11)	0(1)	-0.3(9)	2.6(10)
C9	22.1(11)	24.1(13)	15(1)	-0.3(10)	1.0(9)	0.8(10)
C10	23.5(12)	29.0(15)	22.3(12)	0.4(11)	-3.1(9)	-2.9(11)
C2	26.4(12)	24.2(14)	29.3(14)	-1.2(11)	-3.3(11)	6.8(10)
C4	31.1(13)	34.2(15)	18.0(12)	-1.8(11)	-4.6(10)	5.3(12)
C6	23.8(12)	24.7(13)	16.1(11)	-0.1(10)	-0.7(9)	0.9(10)
C8	24.5(12)	27.6(14)	14.9(11)	-1.5(10)	-0.7(9)	-1.8(10)
C17	27.0(12)	27.3(14)	14.9(11)	-0.7(10)	2.5(10)	0.4(10)
C1	27.0(12)	25.8(13)	19.3(12)	2.8(10)	-4.3(10)	1.8(11)
C16	36.5(15)	28.0(15)	17.1(12)	2.8(11)	3.8(10)	3.6(12)
C25	42.0(17)	33.3(18)	30.4(15)	-12.9(13)	-11.0(13)	8.3(14)
C11	27.7(12)	28.0(14)	20.5(12)	-0.8(11)	0.9(10)	3.4(11)
C19	37.8(16)	36.5(17)	28.7(14)	8.1(13)	-1.1(12)	-8.8(14)
C13	24.8(13)	33.0(16)	27.5(14)	3.4(12)	-1.3(10)	-2.8(11)
C23	35.9(16)	34.6(17)	27.9(14)	-1.5(12)	-0.9(12)	-1.8(13)
C22	35.4(17)	46(2)	44.1(19)	-17.1(17)	8.0(15)	-3.9(15)
C14	23.8(13)	46.1(19)	29.1(14)	2.9(13)	-4.6(11)	1.0(13)
C15	30.5(14)	42.6(18)	21.8(13)	5.2(13)	0.1(11)	11.6(13)
C20	48.4(19)	65(3)	19.7(14)	8.5(15)	-3.1(13)	-25.1(19)
C21	43.3(19)	67(3)	25.1(15)	-14.1(16)	9.4(14)	-21.6(19)
C26	92(3)	47(2)	34.4(19)	-1.3(18)	6(2)	14(2)
C24	37.3(19)	50(3)	93(4)	-26(2)	-19(2)	7.6(18)

Table 4. Bond Lengths for B302_0m.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
S1	O5	1.430(3)	C7	C6	1.493(4)
S1	N2	1.642(2)	C5	C4	1.394(4)
S1	O6	1.429(3)	C5	C6	1.400(4)
S1	C18	1.758(3)	C12	C9	1.514(4)
Cl2	C3	1.734(3)	C12	C17	1.386(4)
Cl1	C5	1.724(3)	C12	C13	1.379(4)
O2	C7	1.358(3)	C9	C8	1.573(4)
O2	C8	1.448(3)	C9	C11	1.551(4)

O3	C10	1.354(4)	C2	C1	1.381(4)
O3	C11	1.442(3)	C6	C1	1.399(4)
O1	C7	1.203(4)	C17	C16	1.383(4)
O4	C10	1.212(4)	C16	C15	1.403(5)
N2	C8	1.454(3)	C25	C26	1.497(6)
N2	C17	1.425(4)	C25	C24	1.487(5)
O7	C25	1.210(4)	C19	C20	1.387(5)
N1	C9	1.445(3)	C13	C14	1.394(4)
N1	C10	1.352(4)	C23	C22	1.391(5)
C3	C2	1.381(4)	C22	C21	1.377(6)
C3	C4	1.380(4)	C14	C15	1.380(5)
C18	C19	1.388(4)	C20	C21	1.376(6)
C18	C23	1.386(5)			

Table 5. Bond Angles for B302_0m.

Atom	**Atom**	**Atom**	**Angle/°**	**Atom**	**Atom**	**Atom**	**Angle/°**
O5	S1	N2	104.78(14)	C12	C9	C11	114.8(2)
O5	S1	C18	108.74(15)	C11	C9	C8	113.5(2)
N2	S1	C18	107.13(13)	O4	C10	O3	122.9(3)
O6	S1	O5	120.29(17)	O4	C10	N1	127.5(3)
O6	S1	N2	107.74(15)	N1	C10	O3	109.6(2)
O6	S1	C18	107.49(16)	C3	C2	C1	118.9(3)
C7	O2	C8	114.1(2)	C3	C4	C5	119.0(2)
C10	O3	C11	109.3(2)	C5	C6	C7	122.2(2)
C8	N2	S1	122.8(2)	C1	C6	C7	119.9(2)
C17	N2	S1	125.23(19)	C1	C6	C5	117.8(2)
C17	N2	C8	111.3(2)	O2	C8	N2	105.9(2)
C10	N1	C9	113.6(2)	O2	C8	C9	110.6(2)
C2	C3	Cl2	120.1(2)	N2	C8	C9	105.1(2)
C4	C3	Cl2	118.4(2)	C12	C17	N2	109.2(2)
C4	C3	C2	121.5(3)	C16	C17	N2	129.0(3)
C19	C18	S1	119.3(3)	C16	C17	C12	121.8(3)
C23	C18	S1	118.8(2)	C2	C1	C6	121.7(2)
C23	C18	C19	121.7(3)	C17	C16	C15	116.7(3)
O2	C7	C6	110.8(2)	O7	C25	C26	120.2(4)
O1	C7	O2	122.5(3)	O7	C25	C24	121.5(4)

O1	C7	C6	126.7(3)	C24	C25	C26	118.4(4)
C4	C5	Cl1	115.2(2)	O3	C11	C9	105.5(2)
C4	C5	C6	121.0(3)	C20	C19	C18	118.6(3)
C6	C5	Cl1	123.8(2)	C12	C13	C14	118.0(3)
C17	C12	C9	111.3(2)	C18	C23	C22	118.3(3)
C13	C12	C9	127.5(3)	C21	C22	C23	120.6(4)
C13	C12	C17	121.1(3)	C15	C14	C13	120.6(3)
N1	C9	C12	112.7(2)	C14	C15	C16	121.7(3)
N1	C9	C8	113.5(2)	C21	C20	C19	120.4(3)
N1	C9	C11	100.1(2)	C20	C21	C22	120.3(3)
C12	C9	C8	102.7(2)				

Table 6. Hydrogen Bonds for B302_0m.

D	**H**	**A**	**d(D-H)/Å**	**d(H-A)/Å**	**d(D-A)/Å**	**D-H-A/°**
N1	H1	O7[1]	0.985(7)	1.909(11)	2.877(3)	167(3)

[1]1+X,+Y,+Z

Table 7. Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for B302_0m.

Atom	***x***	***y***	***z***	**U(eq)**
H2	-1427	-7723	-6571	32
H4	-4065	-5789	-7495	33
H8	-3674	-4307	-4494	27
H1A	-1794	-6631	-5738	29
H16	-618	-6354	-3233	33
H11A	-3144	-2529	-4291	30
H11B	-1658	-2119	-4103	30
H19	-2988	-7000	-2607	41
H13	991	-3018	-4101	34
H23	-5122	-4509	-3406	39
H22	-5940	-3941	-2479	50
H14	2313	-3955	-3387	40
H15	1531	-5594	-2969	38
H20	-3877	-6441	-1694	53

H21	-5369	-4937	-1637	54
H26A	-8508	-6268	-4472	87
H26B	-8681	-7207	-4956	87
H26C	-9859	-6323	-4855	87
H24A	-6475	-5389	-5773	90
H24B	-6446	-6536	-5429	90
H24C	-6240	-5403	-5083	90
H1	-370(30)	-4050(20)	-5318(15)	31(9)

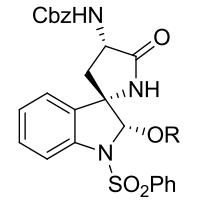
Experimental

Single crystals of $C_{26}H_{22}Cl_2N_2O_7S$ [B302_0m] were []. A suitable crystal was selected and [] on a apex2_Mo diffractometer. The crystal was kept at 173(2) K during data collection. Using Olex2 [1], the structure was solved with the Superflip [2] structure solution program using Charge Flipping and refined with the ShelXL [3] refinement package using Least Squares minimisation.

1. O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, OLEX2: a complete structure solution, refinement and analysis program. J. Appl. Cryst. (2009). 42, 339-341.
2. SHELXS-97 (Sheldrick, 2008)
3. SHELXL-97 (Sheldrick, 2008)

Crystal structure determination of [B302_0m]

Crystal Data for $C_{26}H_{22}Cl_2N_2O_7S$ (M =577.41): orthorhombic, space group $P2_12_12_1$ (no. 19), a = 9.6790(7) Å, b = 11.8883(8) Å, c = 22.4824(16) Å, V = 2587.0(3) Å^3, Z = 4, T = 173(2) K, μ(MoKα) = 0.382 mm^{-1}, *Dcalc* = 1.483 g/mm^3, 20608 reflections measured ($3.624 \leq 2\Theta \leq 61.158$), 7834 unique ($R_{int}$ = 0.0289) which were used in all calculations. The final R_1 was 0.0482 ($I > 2\sigma(I)$) and wR_2 was 0.1218 (all data).



6

R = 2,4-Cl_2-benzoyl

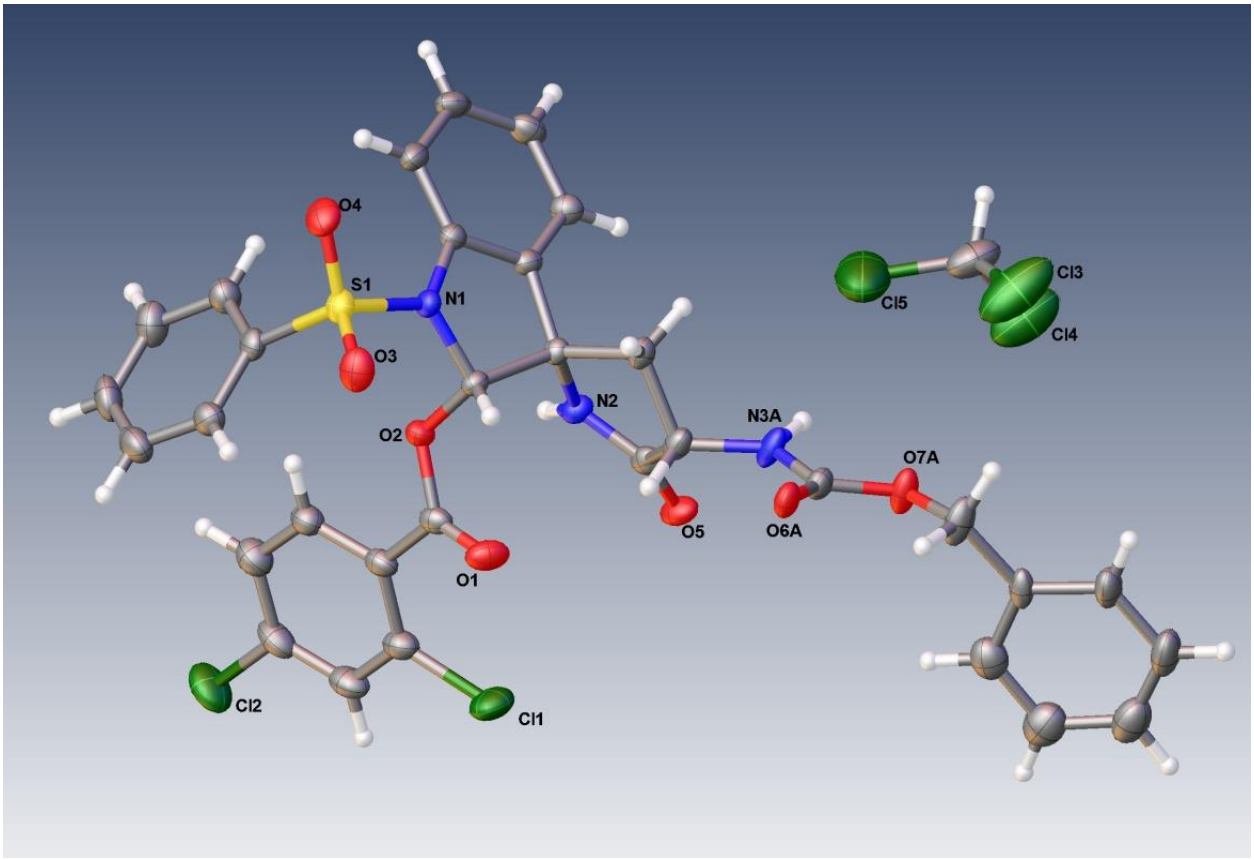


Table 8. Crystal data and structure refinement for trypt

Identification code	trypt
Empirical formula	$C_{33}H_{26}Cl_5N_3O_7S$
Formula weight	785.88
Temperature/K	172.3
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	9.6220(13)
b/Å	18.082(2)
c/Å	19.975(3)

α/°	90
β/°	90
γ/°	90
Volume/Å^3	3475.4(8)
Z	4
ρ_{calc}mg/mm^3	1.502
m/mm^{-1}	0.530
F(000)	1608.0
Crystal size/mm^3	0.928 × 0.331 × 0.19
2Θ range for data collection	4.078 to 63.784°
Index ranges	-14 ≤ h ≤ 13, -26 ≤ k ≤ 18, -28 ≤ l ≤ 25
Reflections collected	30478
Independent reflections	11170[R(int) = 0.0350]
Data/restraints/parameters	11170/158/476
Goodness-of-fit on F^2	1.030
Final R indexes [I>=2σ (I)]	R_1 = 0.0561, wR_2 = 0.1352
Final R indexes [all data]	R_1 = 0.0706, wR_2 = 0.1451
Largest diff. peak/hole / e Å^{-3}	0.65/-0.53
Flack parameter	-0.01(7)

Table 9. Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for trypt. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	***x***	***y***	***z***	**U(eq)**
N3B	-4670(9)	-8722(3)	-4607(5)	31(2)
C24B	-3588(10)	-9184(6)	-4559(8)	26.8(10)
O6B	-2523(6)	-9171(4)	-4891(3)	27.6(9)
O7B	-3834(5)	-9676(3)	-4064(4)	35.7(14)
C25B	-2702(6)	-10190(4)	-3954(3)	39.4(14)
C26B	-3009(9)	-10611(3)	-3316(3)	28.2(15)
C27B	-3103(6)	-11379(3)	-3349(3)	36.4(11)
C28B	-3319(7)	-11785(3)	-2767(3)	46.5(14)
C29B	-3456(9)	-11422(4)	-2168(4)	49.2(14)
C30B	-3411(7)	-10662(5)	-2125(3)	50.2(13)
C31B	-3185(13)	-10261(4)	-2715(3)	41.2(13)
N3A	-4580(20)	-8805(8)	-4729(14)	31(2)

C24A	-3610(20)	-9300(15)	-4522(17)	26.8(10)
O6A	-2406(14)	-9268(10)	-4728(7)	27.6(9)
O7A	-4114(13)	-9848(7)	-4142(9)	35.7(14)
C25A	-3127(14)	-10437(7)	-3971(6)	39.4(14)
C26A	-3280(30)	-10624(6)	-3242(6)	28.2(15)
C27A	-3299(14)	-11352(6)	-3026(6)	36.4(11)
C28A	-3310(20)	-11544(7)	-2355(6)	46.5(14)
C29A	-3306(14)	-10964(6)	-1903(6)	49.2(14)
C30A	-3257(15)	-10230(7)	-2098(6)	50.2(13)
C31A	-3230(30)	-10060(7)	-2774(6)	41.2(13)
S1	-2949.4(8)	-6225.1(4)	-7293.1(4)	24.94(16)
Cl1	-3177.4(12)	-5698.9(6)	-3673.0(4)	45.5(2)
Cl2	-4927.1(14)	-2953.5(6)	-4139.6(6)	55.3(3)
Cl3	-3677(2)	-11782.6(13)	-5566.1(7)	99.3(7)
Cl4	-5967.1(16)	-11143.8(11)	-4841.5(7)	85.2(5)
Cl5	-4615(3)	-10310.4(10)	-5859.4(8)	107.6(7)
O2	-4086(2)	-6043.8(11)	-5829.8(10)	23.2(4)
O4	-3285(3)	-6384.0(14)	-7979.1(12)	35.9(5)
N1	-4122(3)	-6671.1(14)	-6844.3(12)	20.8(5)
O3	-1628(2)	-6429.3(14)	-7021.8(14)	35.7(6)
O5	-5847(3)	-7425.0(15)	-4183.2(11)	33.3(5)
O1	-2767(2)	-6415.7(15)	-4962.9(12)	34.7(5)
N2	-5748(3)	-7039.0(15)	-5275.6(12)	22.4(5)
C7	-3912(3)	-6768.1(16)	-6130.7(13)	18.9(5)
C23	-5431(3)	-7480.3(18)	-4757.6(15)	25.2(6)
C13	-6178(3)	-7158.9(16)	-6486.8(14)	20.9(5)
C20	-5172(3)	-7265.7(15)	-5914.1(13)	19.0(5)
C14	-3169(3)	-5265.3(17)	-7161.0(15)	24.6(6)
C6	-3484(3)	-5952.8(18)	-5219.7(15)	24.5(6)
C12	-7569(3)	-7353.9(18)	-6518.9(16)	26.0(6)
C8	-5534(3)	-6805.8(15)	-7018.3(14)	20.4(5)
C21	-4757(3)	-8081.2(16)	-5772.9(15)	23.6(6)
C22	-4445(3)	-8068.1(18)	-5020.2(16)	27.0(6)
C10	-7662(4)	-6833.0(19)	-7626.2(17)	31.1(7)
C3	-3850(3)	-5214.5(18)	-4940.9(16)	26.7(6)
C11	-8317(3)	-7179.7(19)	-7095.1(17)	31.2(7)
C9	-6258(4)	-6641.9(17)	-7602.4(15)	27.4(6)
C1	-4669(4)	-3963(2)	-5130(2)	38.1(8)

C4	-3720(4)	-5053(2)	-4258.2(16)	31.5(7)
C2	-4329(4)	-4657.1(19)	-5366.5(17)	30.5(7)
C19	-2063(4)	-4859.1(19)	-6907.5(17)	31.9(7)
C15	-4395(4)	-4927.8(18)	-7356.5(18)	31.6(7)
C1D	-4529(4)	-3827(2)	-4447.0(19)	38.0(8)
C16	-4521(4)	-4164(2)	-7287(2)	39.4(8)
C5	-4078(4)	-4362(2)	-4014.5(18)	36.6(8)
C17	-3419(5)	-3754(2)	-7038(2)	42.6(9)
C18	-2199(5)	-4098(2)	-6855.8(19)	41.6(9)
C1L	-5119(6)	-11183(3)	-5618(2)	57.0(12)

Table 10. Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for trypt. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+...+2hka\times b\times U_{12}]$

Atom	**U_{11}**	**U_{22}**	**U_{33}**	**U_{23}**	**U_{13}**	**U_{12}**
N3B	21.3(16)	41(2)	29(5)	20(3)	4.8(17)	2.8(14)
C24B	27.8(14)	26(4)	26(2)	8(2)	-3.7(11)	-0.9(18)
O6B	29.0(14)	24(2)	30(3)	11.3(18)	-1.8(18)	2.8(13)
O7B	22(2)	37(3)	49(2)	24(2)	1.3(18)	3.3(17)
C25B	28(3)	41(3)	49(2)	24(2)	6(2)	10(2)
C26B	16(4)	24.6(14)	43.8(19)	14.4(13)	0.3(18)	-1.7(14)
C27B	34(2)	27.6(17)	48(3)	15(2)	-7(2)	-2.6(16)
C28B	42(3)	40(3)	58(3)	26(2)	-6(2)	-3(2)
C29B	37(3)	59(3)	52(3)	21(2)	-5(2)	0(2)
C30B	39(3)	61(3)	50(2)	10(2)	-1(2)	-3(3)
C31B	32(2)	39(3)	53(2)	4(2)	-1.2(19)	-1(3)
N3A	21.3(16)	41(2)	29(5)	20(3)	4.8(17)	2.8(14)
C24A	27.8(14)	26(4)	26(2)	8(2)	-3.7(11)	-0.9(18)
O6A	29.0(14)	24(2)	30(3)	11.3(18)	-1.8(18)	2.8(13)
O7A	22(2)	37(3)	49(2)	24(2)	1.3(18)	3.3(17)
C25A	28(3)	41(3)	49(2)	24(2)	6(2)	10(2)
C26A	16(4)	24.6(14)	43.8(19)	14.4(13)	0.3(18)	-1.7(14)
C27A	34(2)	27.6(17)	48(3)	15(2)	-7(2)	-2.6(16)
C28A	42(3)	40(3)	58(3)	26(2)	-6(2)	-3(2)
C29A	37(3)	59(3)	52(3)	21(2)	-5(2)	0(2)
C30A	39(3)	61(3)	50(2)	10(2)	-1(2)	-3(3)
C31A	32(2)	39(3)	53(2)	4(2)	-1.2(19)	-1(3)
S1	24.0(3)	27.0(3)	23.8(3)	3.3(3)	7.1(3)	-1.0(3)

Cl1	60.3(6)	53.2(6)	23.1(3)	-3.0(4)	-5.4(4)	2.9(5)
Cl2	72.3(7)	34.0(5)	59.7(6)	-19.4(4)	18.1(6)	-8.8(5)
Cl3	93.4(11)	155.1(17)	49.4(7)	17.6(9)	23.7(7)	66.0(12)
Cl4	71.4(9)	127.9(14)	56.4(7)	8.2(8)	12.6(7)	50.4(10)
Cl5	188(2)	82.3(11)	52.8(8)	-10.8(7)	-8.5(11)	-30.9(13)
O2	25.6(10)	21.9(10)	22.0(9)	-1.4(8)	-3.6(8)	-2.2(8)
O4	45.5(14)	37.9(13)	24.3(11)	0.3(9)	11.5(10)	-2.9(11)
N1	20.9(11)	23.9(12)	17.7(10)	3.6(9)	1.2(8)	-4.8(9)
O3	23.9(11)	37.1(13)	46.1(14)	7.3(11)	8.8(10)	2.9(9)
O5	32.2(12)	50.0(15)	17.7(9)	1.7(9)	1.5(9)	-9.2(11)
O1	29.7(12)	44.9(14)	29.5(11)	-6.3(10)	-7.3(10)	8.6(10)
N2	19.6(11)	29.5(13)	18(1)	0.6(9)	2.4(8)	2.4(9)
C7	19.7(12)	21.5(13)	15.6(11)	0.8(9)	-0.5(9)	0.5(10)
C23	17.7(12)	34.6(16)	23.3(13)	2.0(11)	-0.2(10)	-7.2(11)
C13	23.3(13)	20.2(13)	19.1(12)	-1.1(10)	-2.7(10)	2(1)
C20	18.2(12)	21.9(12)	16.8(11)	0.7(9)	2.3(9)	-1(1)
C14	25.6(14)	24.4(14)	23.7(13)	4.5(10)	4.2(11)	-4.4(11)
C6	19.1(12)	32.3(15)	21.9(13)	-3.5(11)	1.1(10)	-6.0(11)
C12	22.8(13)	29.8(15)	25.6(13)	-1.6(11)	0.6(11)	-0.2(11)
C8	22.3(13)	18.9(12)	20.1(12)	-0.7(10)	-2(1)	-0.8(10)
C21	24.6(13)	22.1(13)	24.1(13)	4.3(10)	0.3(11)	1.7(11)
C22	22.2(13)	33.3(16)	25.6(14)	10.6(12)	-1.8(11)	-2.1(12)
C10	35.2(17)	29.2(15)	29.1(15)	-1.8(12)	-13.8(13)	0.5(13)
C3	24.8(14)	30.4(16)	24.7(13)	-5.7(11)	1.5(11)	-8.1(12)
C11	24.1(15)	31.4(16)	38.1(17)	-4.2(13)	-7.3(13)	-1.4(12)
C9	37.2(16)	22.9(14)	22.1(13)	1.5(11)	-5.7(12)	-1.9(12)
C1	40.5(19)	33.7(18)	40.2(19)	-5.6(14)	3.8(15)	-4.8(15)
C4	31.8(16)	37.8(18)	24.9(14)	-4.6(13)	-0.5(12)	-7.5(14)
C2	33.9(17)	30.8(16)	26.9(15)	-3.2(12)	-0.1(12)	-6.5(13)
C19	29.3(15)	34.3(17)	32.1(15)	4.2(13)	-1.2(13)	-8.0(13)
C15	31.1(15)	27.9(15)	35.8(16)	1.6(13)	-1.1(13)	-1.9(12)
C1D	40.3(18)	32.2(17)	41.4(19)	-14.0(15)	9.4(15)	-10.6(15)
C16	39.7(19)	30.1(17)	48(2)	7.7(15)	6.6(16)	3.0(14)
C5	38.4(18)	42.0(19)	29.6(16)	-12.4(14)	4.1(14)	-9.8(15)
C17	57(2)	23.3(16)	48(2)	3.6(15)	11.7(18)	-8.3(16)
C18	49(2)	38(2)	37.3(18)	-1.4(14)	1.6(17)	-19.8(17)
C1L	63(3)	74(3)	33.5(19)	0(2)	-10.2(19)	15(3)

Table 11. Bond Lengths for trypt.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
N3B	C24B	1.338(8)	O2	C7	1.451(3)
N3B	C22	1.459(4)	O2	C6	1.359(4)
C24B	O6B	1.221(8)	N1	C7	1.450(3)
C24B	O7B	1.352(8)	N1	C8	1.424(4)
O7B	C25B	1.447(7)	O5	C23	1.219(4)
C25B	C26B	1.515(7)	O1	C6	1.200(4)
C26B	C27B	1.393(7)	N2	C23	1.342(4)
C26B	C31B	1.367(8)	N2	C20	1.450(4)
C27B	C28B	1.390(8)	C7	C20	1.570(4)
C28B	C29B	1.372(10)	C23	C22	1.518(5)
C29B	C30B	1.376(11)	C13	C20	1.511(4)
C30B	C31B	1.400(9)	C13	C12	1.386(4)
N3A	C24A	1.357(15)	C13	C8	1.385(4)
N3A	C22	1.460(5)	C20	C21	1.553(4)
C24A	O6A	1.234(16)	C14	C19	1.389(4)
C24A	O7A	1.338(14)	C14	C15	1.385(5)
O7A	C25A	1.466(13)	C6	C3	1.489(5)
C25A	C26A	1.503(13)	C12	C11	1.394(4)
C26A	C27A	1.386(6)	C8	C9	1.390(4)
C26A	C31A	1.385(6)	C21	C22	1.533(4)
C27A	C28A	1.385(6)	C10	C11	1.384(5)
C28A	C29A	1.385(6)	C10	C9	1.396(5)
C29A	C30A	1.383(6)	C3	C4	1.400(4)
C30A	C31A	1.385(6)	C3	C2	1.397(5)
S1	O4	1.437(3)	C1	C2	1.380(5)
S1	N1	1.651(2)	C1	C1D	1.394(5)
S1	O3	1.430(3)	C4	C5	1.385(5)
S1	C14	1.768(3)	C19	C18	1.386(5)
Cl1	C4	1.732(4)	C15	C16	1.394(5)
Cl2	C1D	1.738(4)	C1D	C5	1.368(6)
Cl3	C1L	1.764(5)	C16	C17	1.386(6)
Cl4	C1L	1.754(5)	C17	C18	1.377(6)
Cl5	C1L	1.720(6)			

Table 12. Bond Angles for trypt.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C24B	N3B	C22	115.5(5)	C8	C13	C12	120.9(3)
N3B	C24B	O7B	109.1(7)	N2	C20	C7	112.1(2)
O6B	C24B	N3B	127.1(6)	N2	C20	C13	112.6(2)
O6B	C24B	O7B	123.8(6)	N2	C20	C21	102.0(2)
C24B	O7B	C25B	113.7(5)	C13	C20	C7	102.3(2)
O7B	C25B	C26B	107.7(5)	C13	C20	C21	115.1(2)
C27B	C26B	C25B	118.3(6)	C21	C20	C7	113.3(2)
C31B	C26B	C25B	122.0(5)	C19	C14	S1	118.8(3)
C31B	C26B	C27B	119.7(6)	C15	C14	S1	119.5(2)
C28B	C27B	C26B	119.7(6)	C15	C14	C19	121.5(3)
C29B	C28B	C27B	119.5(6)	O2	C6	C3	110.1(3)
C28B	C29B	C30B	121.9(7)	O1	C6	O2	122.9(3)
C29B	C30B	C31B	118.0(7)	O1	C6	C3	127.0(3)
C26B	C31B	C30B	121.2(6)	C13	C12	C11	118.7(3)
C24A	N3A	C22	131.4(15)	C13	C8	N1	108.6(2)
O6A	C24A	N3A	120.9(13)	C13	C8	C9	121.2(3)
O6A	C24A	O7A	124.3(13)	C9	C8	N1	130.3(3)
O7A	C24A	N3A	114.4(13)	C22	C21	C20	102.3(2)
C24A	O7A	C25A	115.9(11)	N3B	C22	C23	106.2(4)
O7A	C25A	C26A	109.0(12)	N3B	C22	C21	120.9(6)
C27A	C26A	C25A	121.2(10)	N3A	C22	C23	116.4(8)
C31A	C26A	C25A	119.0(9)	N3A	C22	C21	111.1(13)
C31A	C26A	C27A	119.4(10)	C23	C22	C21	103.1(2)
C28A	C27A	C26A	122.7(10)	C11	C10	C9	121.8(3)
C29A	C28A	C27A	116.2(11)	C4	C3	C6	122.0(3)
C30A	C29A	C28A	122.9(11)	C2	C3	C6	119.8(3)
C29A	C30A	C31A	119.3(11)	C2	C3	C4	118.2(3)
C30A	C31A	C26A	119.6(10)	C10	C11	C12	120.0(3)
O4	S1	N1	105.48(14)	C8	C9	C10	117.4(3)
O4	S1	C14	108.17(15)	C2	C1	C1D	118.1(4)
N1	S1	C14	108.46(13)	C3	C4	Cl1	123.0(3)
O3	S1	O4	120.61(16)	C5	C4	Cl1	116.5(3)
O3	S1	N1	105.98(14)	C5	C4	C3	120.5(3)
O3	S1	C14	107.64(16)	C1	C2	C3	121.8(3)
C6	O2	C7	115.6(2)	C18	C19	C14	118.7(3)
C7	N1	S1	119.87(19)	C14	C15	C16	118.9(3)

C8	N1	S1	127.1(2)	C1	C1D	Cl2	119.0(3)
C8	N1	C7	110.6(2)	C5	C1D	Cl2	119.3(3)
C23	N2	C20	115.0(3)	C5	C1D	C1	121.7(3)
O2	C7	C20	108.3(2)	C17	C16	C15	119.9(4)
N1	C7	O2	106.4(2)	C1D	C5	C4	119.7(3)
N1	C7	C20	103.5(2)	C18	C17	C16	120.4(4)
O5	C23	N2	127.0(3)	C17	C18	C19	120.6(4)
O5	C23	C22	126.0(3)	Cl4	C1L	Cl3	109.8(3)
N2	C23	C22	107.0(2)	Cl5	C1L	Cl3	111.0(3)
C12	C13	C20	128.4(3)	Cl5	C1L	Cl4	110.0(3)
C8	C13	C20	110.7(2)				

Table 13. Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for trypt.

Atom	***x***	***y***	***z***	**U(eq)**
H3B	-5464	-8807	-4402	37
H25A	-1814	-9918	-3911	47
H25B	-2626	-10536	-4336	47
H27B	-3020	-11625	-3768	44
H28B	-3370	-12309	-2784	56
H29B	-3586	-11702	-1771	59
H30B	-3530	-10418	-1708	60
H31B	-3153	-9737	-2697	49
H3A	-5446	-8954	-4678	37
H25C	-2166	-10269	-4063	47
H25D	-3315	-10880	-4248	47
H27A	-3301	-11735	-3352	44
H28A	-3331	-12046	-2213	56
H29A	-3335	-11074	-1438	59
H30A	-3244	-9848	-1772	60
H31A	-3173	-9559	-2915	49
H2	-6268	-6641	-5231	27
H7	-2993	-6997	-6022	23
H12	-8004	-7601	-6155	31
H21A	-5529	-8424	-5877	28
H21B	-3926	-8226	-6034	28
H22A	-3468	-7894	-4953	32
H22	-3468	-7894	-4953	32

H10	-8183	-6722	-8018	37
H11	-9277	-7299	-7123	37
H9	-5813	-6409	-7971	33
H1	-4990	-3588	-5426	46
H2A	-4424	-4759	-5831	37
H19	-1229	-5098	-6772	38
H15	-5139	-5212	-7535	38
H16	-5360	-3924	-7412	47
H5	-4010	-4260	-3549	44
H17	-3507	-3234	-6991	51
H18	-1444	-3811	-6693	50
H1L	-5782	-11383	-5959	68

Experimental

Single crystals of $C_{33}H_{26}Cl_5N_3O_7S$ [trypt] were []. A suitable crystal was selected and [] on a apex2_Mo diffractometer. The crystal was kept at 172.3 K during data collection. Using Olex2 [1], the structure was solved with the Superflip [2] structure solution program using Charge Flipping and refined with the ShelXL [3] refinement package using Least Squares minimisation.

1. O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, OLEX2: a complete structure solution, refinement and analysis program. J. Appl. Cryst. (2009). 42, 339-341.
2. SHELXS-97 (Sheldrick, 2008)
3. SHELXL-97 (Sheldrick, 2008)

Crystal structure determination of [trypt]

Crystal Data for $C_{33}H_{26}Cl_5N_3O_7S$ (M =785.88): orthorhombic, space group $P2_12_12_1$ (no. 19), a = 9.6220(13) Å, b = 18.082(2) Å, c = 19.975(3) Å, V = 3475.4(8) Å^3, Z = 4, T = 172.3 K, μ(MoKα) = 0.530 mm^{-1}, *Dcalc* = 1.502 g/mm^3, 30478 reflections measured ($4.078 \leq 2\Theta \leq$

63.784), 11170 unique (R_{int} = 0.0350) which were used in all calculations. The final R_1 was 0.0561 (I >2σ(I)) and wR_2 was 0.1451 (all data).